VOLUME 98 • SEPTEMBER 1959 • NUMBER 3

A.M.A. JOURNAL OF

DISEASES OF CHILDREN

Studies on the Genetic Mechanism of Cystic Fibrosis of the Pancreas
Marvin Smoller and David Yi-Yung Hsia

Testosterone-Induced Remission in Aplastic Anemia
Nasrollah T. Shahidi and Louis K. Diamond

Emotional and Personality Development in Neuromuscular Disorders
Marvin L. Blumberg

Giardiasis, a Cause of Celiac Syndrome
Jean A. Cortner

Chylous Ascites and Lymphedema
Warren J. Warwick, Ralph T. Holman, Paul G. Quie, and Robert A. Good

Serum Proteins in Childhood Tuberculosis
Charlotte Marker Zitrin, Edith M. Lincoln, Rosario Carretero, and Enriqueta Melly

Diabetes Mellitus or the Prediabetic State in the Mother and the Neonate
I. F. Gittleman, J. B. Pincus, E. Schmertzler, and F. Annecchiarico

Incidence of Viral Parotitis in the Domestic Dog
Frank Noice, F. M. Bolin, and D. F. Eveleth

Hereditary Hematuria
Edwin P. Russell and Nathan J. Smith

Neonatal Hepatitis
Roy G. Shorter, Archie H. Baggenstoss, and George B. Logan

The Natural History of Mental Deficiency in a State Hospital
George Tarjan, Stanley W. Wright, Harvey F. Dingman, and Georges Sabagh

Mima Polymorpha Meningitis
Charles L. Waite and Allen H. Kline

Congenital Absence of Most of the Colon
Zafar Husain Zaidi

Abstracts from Current Literature

News and Comment

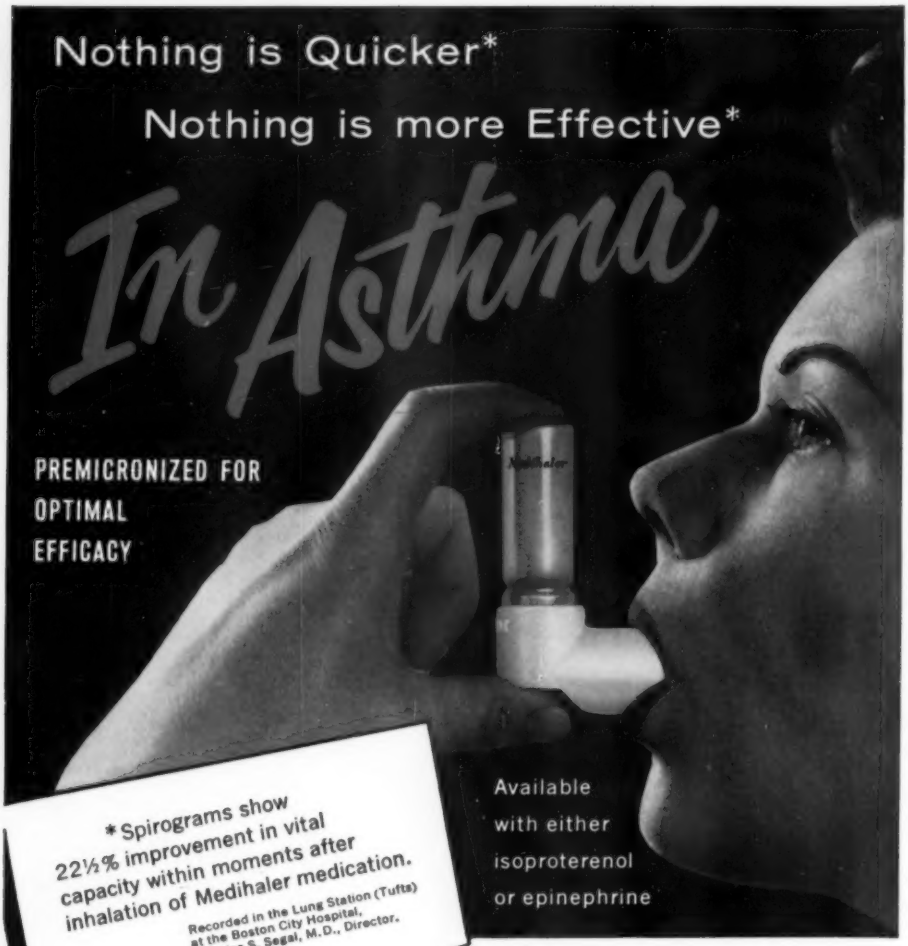
Books

AMERICAN MEDICAL ASSOCIATION PUBLICATION

Nothing is Quicker*

Nothing is more Effective*

In Asthma



PREMICRONIZED FOR OPTIMAL EFFICACY

*Spirograms show 22½% improvement in vital capacity within moments after inhalation of Medihaler medication.

Recorded in the Lung Station (Tufts) at the Boston City Hospital, Maurice S. Segal, M.D., Director.

Available with either isoproterenol or epinephrine

Automatically measured-dose aerosol medications.
Nonbreakable...Shatterproof
Spillproof...Leakproof

Medihaler-ISO®

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.

Medihaler-EPI®

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

NOTABLY WELL TOLERATED AND EFFECTIVE FOR CHILDREN, TOO

Riker Northridge, Calif.

TABLE OF CONTENTS

VOLUME 98 SEPTEMBER 1959 NUMBER 3

ORIGINAL ARTICLES

PAGE

Studies on the Genetic Mechanism of Cystic Fibrosis of the Pancreas
Marvin Smoller, M.D., and David Yi-Yung Hsia, M.D., Chicago 277

Testosterone-Induced Remission in Aplastic Anemia
Nasrollah T. Shahidi, M.D., and Louis K. Diamond, M.D., Boston 293

Emotional and Personality Development in Neuromuscular Disorders
Marvin L. Blumberg, M.D., Rego Park, Long Island, N. Y. 303

Giardiasis, a Cause of Celiac Syndrome
Jean A. Cortner, M.D., Nashville, Tenn. 311

Chylous Ascites and Lymphedema
Warren J. Warwick, M.D.; Ralph T. Holman, Ph.D.; Paul G. Quie, M.D., and Robert A. Good, Ph.D., M.D., Minneapolis 317

Serum Proteins in Childhood Tuberculosis
Charlotte Marker Zitrin, M.D.; Edith M. Lincoln, M.D.; Rosario Carretero, M.D., and Enriqueta Melly, M.D., New York 330

Diabetes Mellitus or the Prediabetic State in the Mother and the Neonate
I. F. Gittleman, M.D.; J. B. Pincus, M.D.; E. Schmertzler, B.S., and F. Annecchiarico, Brooklyn 342

Incidence of Viral Parotitis in the Domestic Dog
Frank Noice, Ph.D.; F. M. Bolin, D.V.M., and D. F. Eveleth, Ph.D., D.V.M., Fargo, N. D. 350

Hereditary Hematuria
Edwin P. Russell, M.D., Los Angeles, and Nathan J. Smith, M.D., Madison, Wis. 353

Neonatal Hepatitis
Roy G. Shorter, M.D.; Archie H. Baggenstoss, M.D., and George B. Logan, M.D., Rochester, Minn. 359

The Natural History of Mental Deficiency in a State Hospital
George Tarjan, M.D.; Stanley W. Wright, M.D.; Harvey F. Dingman, Ph.D., and Georges Sabagh, Ph.D., Pomona, Calif. 370

CASE REPORTS

Mima Polymorpha Meningitis
Comdr. Charles L. Waite (MC), U. S. N., and Lt. Allen H. Kline (MC), U. S. N. R. 379

Congenital Absence of Most of the Colon
Zafar Husain Zaidi, M.B., B.S. (Lucknow), Ottawa, Canada 385

REGULAR DEPARTMENTS

Abstracts from Current Literature 388

News and Comment 408

Books 410

A. M. A.
Journal of Diseases of Children

VOLUME 98 SEPTEMBER 1959 NUMBER 3

COPYRIGHT, 1959, BY THE AMERICAN MEDICAL ASSOCIATION

Published under the Auspices of the Board of Trustees

EDITORIAL BOARD

RICHARD L. DAY, Chief Editor
State University of New York College of Medicine, Downstate Medical Center
450 Clarkson Ave., Brooklyn 3

ROBERT A. ALDRICH, Seattle
ROGER L. J. KENNEDY, Rochester, Minn.
ROBERT B. LAWSON, Miami, Fla.
FRANCIS SCOTT SMYTH, San Francisco
A. A. WEECH, Cincinnati
WARREN E. WHEELER, Columbus, Ohio
JAMES L. WILSON, Ann Arbor, Mich.
WOLF W. ZUELZER, Detroit

ASSOCIATE EDITORS

SYDNEY S. GELLIS, Boston
ROBERT A. GOOD, Minneapolis
ROBERT JACKSON, Columbia, Mo.
VINCENT C. KELLEY, Seattle
C. HENRY KEMPE, Denver
STUART S. STEVENSON, Jersey City, N. J.

J. F. HAMMOND, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals
T. F. RICH, Assistant Managing Editor, Specialty Journals

The A. M. A. Journal of Diseases of Children is published monthly by the American Medical Association and is an official publication of the Association.

Executive Vice President: F. J. L. BLASINGAME, M.D.
Business Manager: RUSSELL H. CLARK

ADVERTISING: Business Director, Russell H. Clark; Advertising Production Manager, Walter H. Kimotek. Advertising Representatives: Vernon J. Wendt, 535 North Dearborn Street, Chicago 10, Illinois, WHitehall 4-1500; Al Detwiller, 475 Fifth Avenue—Room 1005, New York 17, New York, ORegon 9-9383; Dale B. Clarke, 1919 Wilshire Blvd., Los Angeles 57, California, HUbbard 3-3811.

CIRCULATION: Circulation Manager, Robert A. Enlow; Assistant Circulation Manager, Bernard F. Kroeger. The yearly subscription rate of the Journal of Diseases of Children is: U. S. and Possessions, $12.00; Canada $12.50. Other Foreign Countries, $13.50. Special price to Students, Interns, and Residents in U. S. and Possessions, $7.00. Single copies of this and previous calendar year $1.25.

Back issues older that two years are available through Walter J. Johnson, Inc., 111 Fifth Avenue, New York 3, New York. Reprints of back issues available through Johnson Reprint Corporation, 111 Fifth Avenue, New York 3, New York.

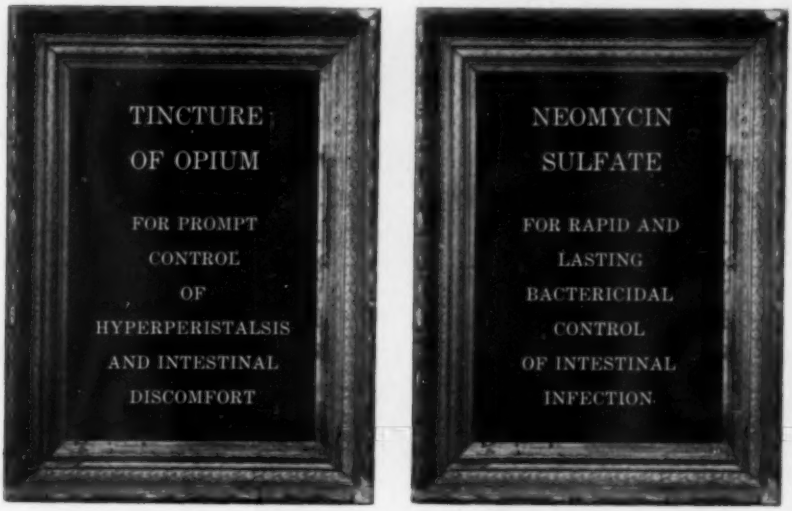
CHANGE OF ADDRESS: Please notify publisher at least six weeks in advance, including both old and new address, and a mailing label taken from the most recent copy. Include your new Postal Zone number, if you live in a zoned city.

Second-class postage paid in Nashville, Tennessee.

Please address communications and subscription orders to: American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

DUOCLASSIC ANTIDIARRHEAL

Now For The First Time: These Two Highly Effective Antidiarrheal Agents Providing Complementary Actions In One Convenient, Delicious, Dosage Form.


TINCTURE OF OPIUM
FOR PROMPT CONTROL OF HYPERPERISTALSIS AND INTESTINAL DISCOMFORT
NEOMYCIN SULFATE
FOR RAPID AND LASTING BACTERICIDAL CONTROL OF INTESTINAL INFECTION

NEW! # PAREMYCIN®

Antibiotic / Antiperistaltic

Brand of Neomycin Sulfate and Tincture of Opium **ELIXIR**

"Paremycin (tincture of opium and neomycin sulfate in combination) provided prompt,... relief of hyperperistalsis and other intestinal discomfort with rapid, lasting pathogenic control."[1]

- Clinically proven in diarrheas of various etiology and in all age groups
- Rapid clinical control
  —after only 1-4 doses and within 12 hours
- Convenient small doses—only ½-2 teaspoonfuls q.i.d. in infants and children
- Delicious banana flavor—clear, non-chalky, non-bulky.

SUPPLIED: Bottles of 6 and 3 fl. oz.

CITED REFERENCE: 1. Schneider, A. J.: The Symptomatic Relief of Pediatric Gastrointestinal Disturbances with Paremycin. (To be submitted for publication).

THE G. F. HARVEY COMPANY, INC. PHARMACEUTICALS AND RESEARCH IN THE HARVEY TRADITION / NEW YORK 10, NEW YORK

SINCE 1900

© Copyright 1959, The G. F. Harvey Company, Inc.

Instructions to Contributors

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor. Articles are accepted for publication on condition that they are contributed solely to this journal.

An original typescript of an article, with one carbon copy, should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. Another carbon copy should be retained by the author.

The main title of an article may not contain more than eighty characters and spaces; a subtitle may be of any length.

The author's name should be accompanied by the highest earned academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

If it is necessary to publish a recognizable photograph of a person, the author should notify the publisher that permission to publish has been obtained from the subject himself if an adult, or from the parents or guardian if a child. An illustration that has been published in another publication should be accompanied by a statement that permission for reproduction has been obtained from the author and the original publisher.

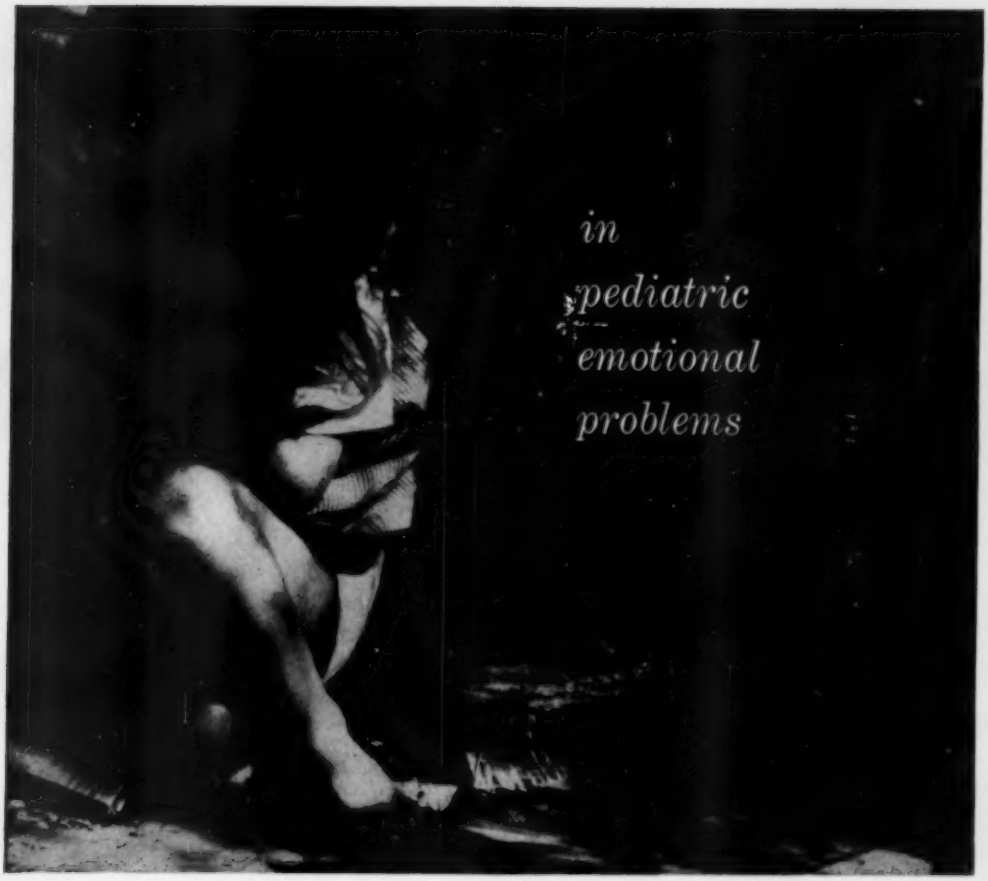
Oversized original illustrations should be photographed and a print on glossy paper submitted. Prints of a bluish tinge should be avoided. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author. The author should submit duplicate prints of roentgenograms and photomicrographs with the essential parts that are to be emphasized circled, as a guide to the photoengraver.

Charts and drawings should be in black ink on hard, white paper. Lettering should be large enough, uniform, and sharp enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, and an abbreviated title of the article, and plainly indicating the top. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be limited to those used by the author in preparation of the article. They should be typed on a special page at the end of the manuscript. The citation should include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. References to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**



new

VISTARIL® *oral suspension*

hydroxyzine pamoate

FULL-RANGE PSYCHOTHERAPEUTIC AGENT

The combination of dependable calming action with relative freedom from side effects makes VISTARIL a drug of choice in a variety of pediatric emotional problems.

DELICIOUSLY LEMON-FLAVORED VISTARIL ORAL SUSPENSION

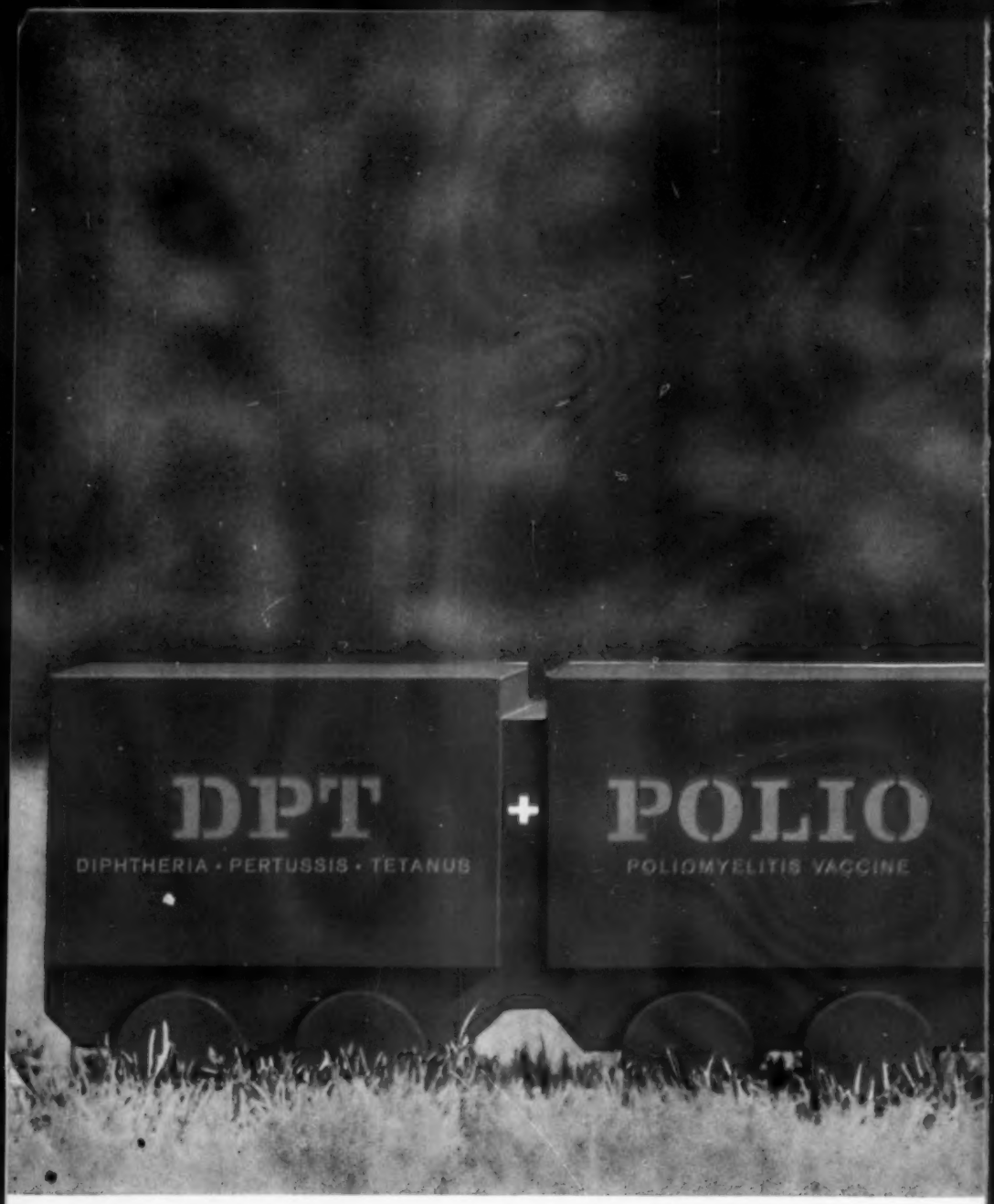
Easy to give and pleasant to take, prescribed at 50-100 mg. daily in divided doses, VISTARIL oral suspension will effectively relieve anxious or hyperkinetic children, pediatric neurosis, stuttering, and tics.

Supply: **Oral Suspension — 25 mg. per 5-cc. teaspoonful. Capsules — 25 mg., 50 mg. and 100 mg. Parenteral Solution — 10-cc. vials and 2-cc. Steraject® Cartridges, each cc. contains 25 mg. hydroxyzine (as the HCl).**

More than a tranquilizer

Pfizer *Science for the world's well-being™*

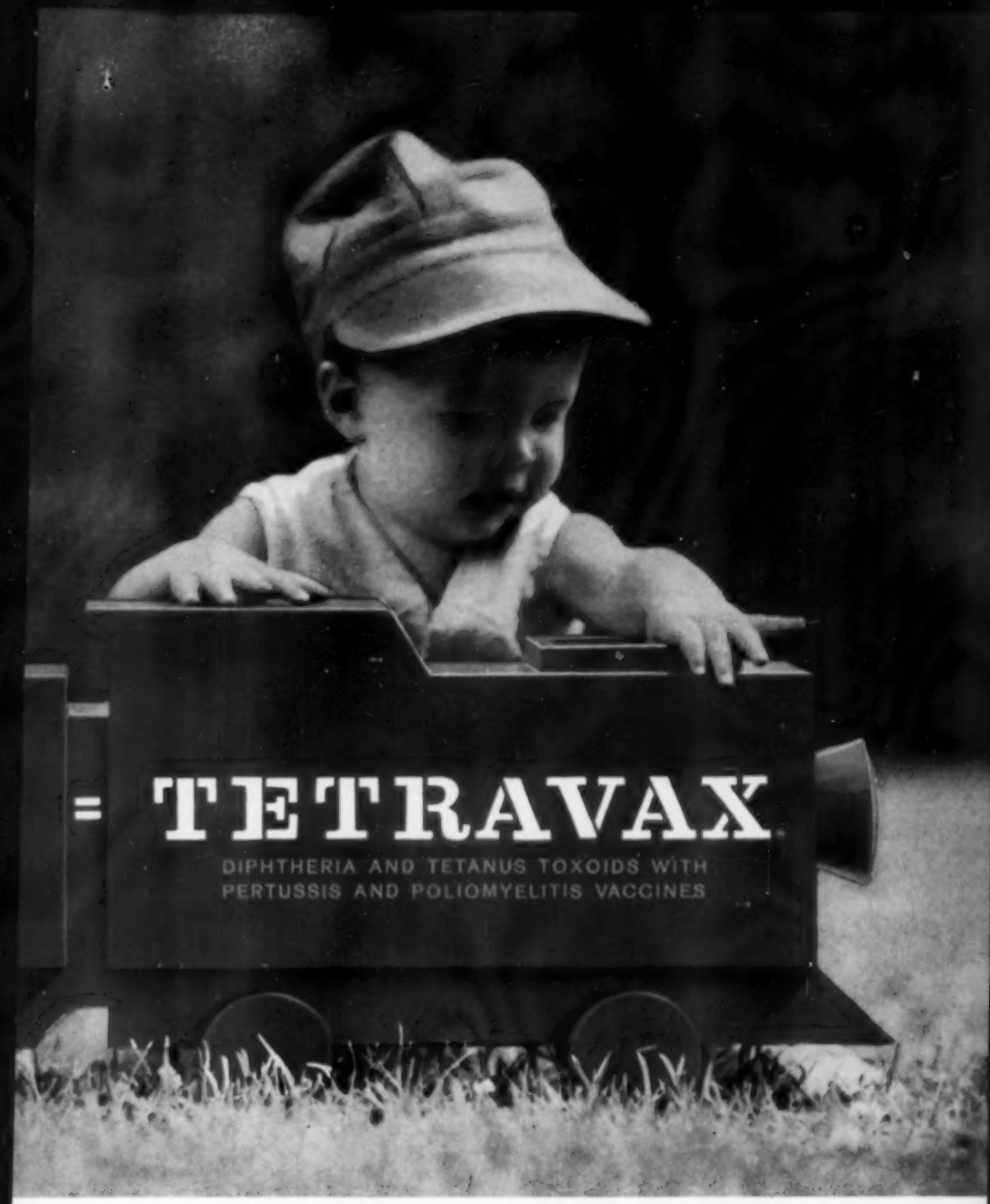
Pfizer Laboratories Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York



FOR SIMULTANEOUS IMMUNIZATION

against 4 diseases:

Poliomyelitis – Diphtheria – Pertussis – Tetanus



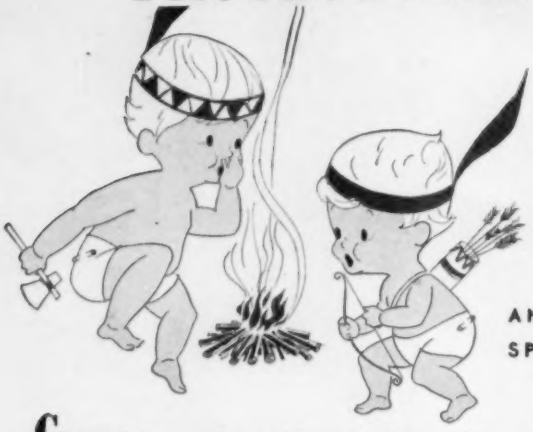
now immunization is possible against more *diseases — with* fewer *injections*

Dosage: 1 cc. *Supplied:* 9 cc. vials in *clear plastic* cartons. Package circular and material in vial can be examined without damaging carton. Expiration date is on vial for checking even if carton is discarded.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

TETRAVAX IS A TRADEMARK OF MERCK & CO., INC.

PROTECT Little Braves' Scalps



WITH
CRADOL®
SPECIFIC
FOR CRADLE CAP

ANOTHER FINE PEDIATRIC
SPECIALTY BY BREON

CRADOL is an antibacterial penetrating emulsion with Diaparene® Chloride (methylbenzethonium chloride) in an oxycholesterin absorption base of liquid petrolatum and lanolin. The absence of keratolytic agents renders it particularly satisfactory for the prevention and treatment of cradle cap.*

*Passchoff, H.D. and Maffia, A.J., "A New Treatment for Cradle Cap", N.Y. State Med., 57:265-267, Jan. 15, 1957.

HOMEMAKERS PRODUCTS DIVISION
George A. Breon & Company, 1450 Broadway, New York 18, N.Y.

---

for infants...
and growing children

Tasty "Junket" rennet-custards furnish more of the nutrients of fresh milk than typical canned "baby desserts."

junket®
RENNET POWDER
makes fresh milk into rennet-custards
—7 tempting flavors

"JUNKET" Reg. U.S. Pat. Off. for rennet and other food products mfd. by Salada-Shirriff-Horsey Inc.

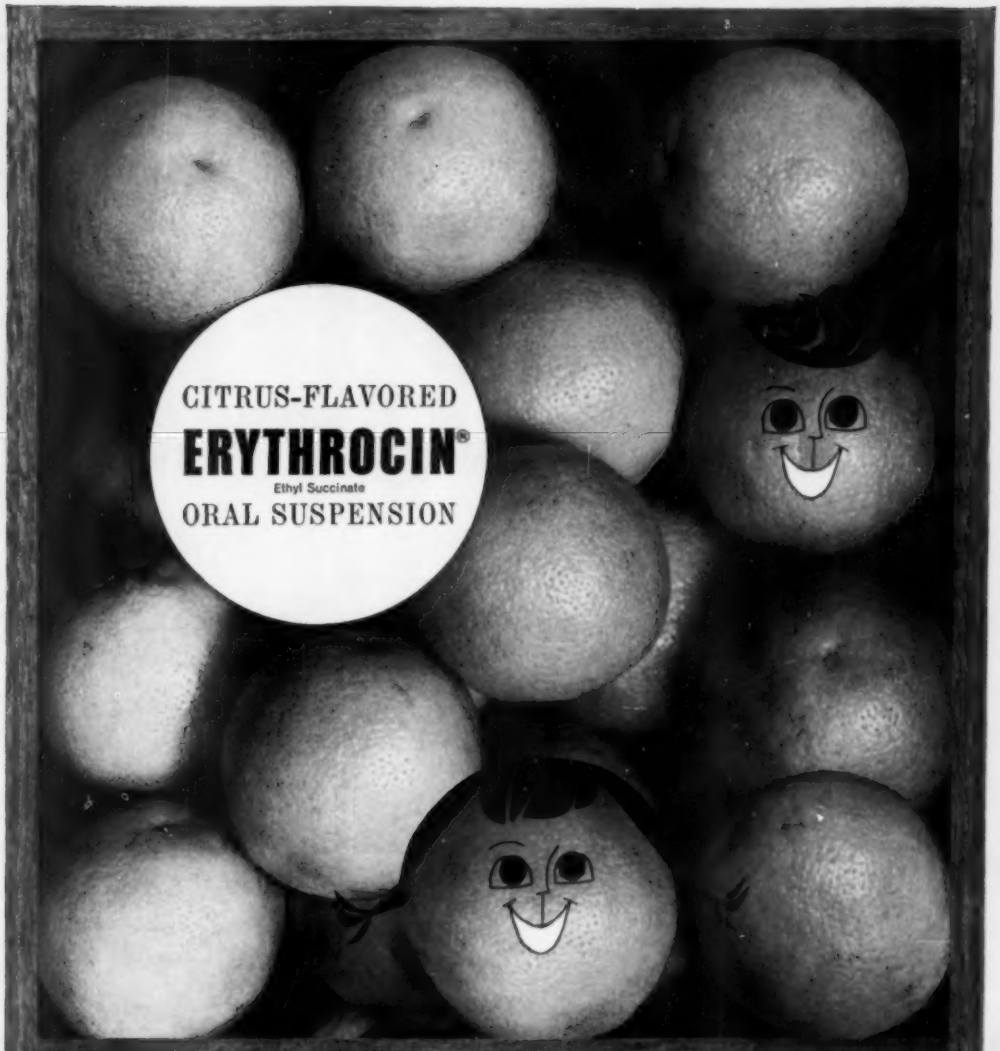
Of interest to you and your patients

THE MENACE OF ALLERGIES

WHAT WE KNOW ABOUT ALLERGY
by Louis Tuft, 12 pages, 15 cents
HOUSE DUST ALLERGY
by Karl D. Figley, 8 pages, 15 cents
FOOD ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents
SKIN ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents
ASTHMA AND HAY FEVER
by Samuel M. Feinberg, M.D., 6 pages, 10 cents
RAGWEED AND HAY FEVER
by Oren C. Durham, 2 pages, 5 cents

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street • Chicago 10 • Illinois

no turned-up noses
at this new Erythrocin Suspension



So sweet and good they can't tell it's "medicine"
It's absolutely delicious! There's no bitterness, no unpleasant aftertaste—just pure, sweet citrus flavor.

So well tolerated and effective you can prescribe it with confidence
After millions of prescriptions, Erythrocin has an unparalleled safety record. High, peak blood levels within one hour—plus well-documented effectiveness against coccal infections.

ABBOTT

®Erythrocin—Erythromycin, Abbott 800128

DIPHTHERIA
TETANUS
PERTUSSIS
POLIO

NEW multiple antigen for pediatric use

QUADRIGEN®

(Diphtheria-Tetanus-Pertussis-Poliomyelitis, Aluminum Phosphate Adsorbed, Parke-Davis)

immunizes against 4 diseases

A newly developed multiple antigen, QUADRIGEN is designed for simultaneous immunization of infants and preschool children against diphtheria, tetanus, pertussis, and paralytic poliomyelitis.

Good antibody response has been demonstrated in children immunized with QUADRIGEN within this age group.*

The antigens in QUADRIGEN are adsorbed on optimum amounts of aluminum phosphate to provide a potent and compatible product.

A single dose of QUADRIGEN is only 0.5 cc. See package for dosage schedule.

With QUADRIGEN, multiple protection can be obtained with fewer injections at low dosage levels—a regimen that appeals both to patients and parents.

*Barrett, C. D., Jr., *et al.*: *J.A.M.A.* 167:1103, 1958; *Ibid.*; Am. J. Pub. Health 49:644, 1959.

Parke, Davis & Company
Detroit 32, Michigan

68459

BAYER

BAYER

1¼ Grs. Ea.
FLAVORED

Living up to a family tradition

There are probably certain medications which are special favorites of yours, medications in which you have a particular confidence.

Physicians, through ever increasing recommendation, have long demonstrated their confidence in the efficacy, potency and purity of Bayer Aspirin, the world's first aspirin.

And the same manufacturing skill, the same 106 ingredient and product tests, the same exclusive processes which contribute to the unsurpassed quality of Bayer Aspirin set the standards of excellence for Bayer Aspirin for Children.

You can depend on Bayer Aspirin for Children for it has been conscientiously formulated to be a pleasant tasting aspirin and to live up to the Bayer family tradition of providing as fine an aspirin as the world has ever known.

Bayer Aspirin for Children—1¼ grain flavored tablets—Supplied in bottles of 50.

● We welcome your requests for samples on Bayer Aspirin and Flavored Bayer Aspirin for Children.

New Tamper-Proof Cap

THE BAYER COMPANY, DIVISION OF STERLING DRUG INC., 1450 BROADWAY, NEW YORK 18, N. Y.

vitamin protection

...for engineers

or career women

the multivitamin in the pleasant tasting

SOFTAB® *form*

Mulvidren®

melts in the mouth
no water needed

or physicians

or ball players

EACH TABLET CONTAINS:

VITAMINS

A	5,000 USP Units
D	1,000 USP Units
C	60 mg.
B_1	2 mg.
B_2	2 mg.
B_6	1 mg.
B_{12} as Iocon-12*	3 mcg.
d-Calcium Pantothenate	3 mg.
Nicotinamide	10 mg.

*Iocon Stuart Iocon-12 increases Vitamin B_{12} absorption from food.

DOSAGE: 1 tablet daily or more as directed by physician.

AVAILABLE: Bottles of 30 & 100 tablets at all pharmacies.

Stuart

THE STUART COMPANY • PASADENA, CALIFORNIA

Of interest to you and your patients

THE MENACE OF ALLERGIES

WHAT WE KNOW ABOUT ALLERGY
by Louis Tuft, 12 pages, 15 cents

HOUSE DUST ALLERGY
by Karl D. Figley, 8 pages, 15 cents

FOOD ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

SKIN ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

ASTHMA AND HAY FEVER
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

RAGWEED AND HAY FEVER
by Oren C. Durham, 2 pages, 5 cents

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10 • ILLINOIS

NOW AVAILABLE

1958 EDITION

A.M.A. HEALTH PUBLICATIONS CATALOG

HEALTH PROBLEMS
MEDICAL CARE
MEDICAL EDUCATION AND HOSPITALS
MEDICAL ECONOMICS

SEND FOR YOUR
FREE
COPY

BUREAU OF HEALTH EDUCATION
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

NOW YOU can prescribe Meyenberg *Powdered* Goat Milk, and your patients can get it anywhere. Palatable and portable, Meyenberg *Powdered* is extra convenient for traveling... and costs less. Like Meyenberg *Evaporated,* Meyenberg *Powdered* Goat Milk is a medication of choice for cow's milk allergy. In some cases, however, it is preferable to prescribe Meyenberg *Powdered*—as in the case of older children. Because Meyenberg *Powdered* tastes just like dairy-fresh milk, the transition from cow's to goat's milk is a naturally simple one. *Powdered* or *Evaporated,* Meyenberg Goat Milk is nutritionally equal to cow's milk in protein, fat, carbohydrate and minerals. It provides a fine soft curd, readily digestible and free of crude fibers which may cause diarrhea. Always specify Meyenberg, your assurance of goat milk of the highest, most dependable quality. By Jackson-Mitchell Pharmaceuticals, Inc.—serving the medical profession for 25 years.

Formulae — MEYENBERG *Powdered* GOAT MILK

	POWDER	WATER	CALORIES FL. OZ.
Introductory or Transitional	1 Tablespoon	3 Fl. Oz.	14
Standard Formula	1 Tablespoon	2 Fl. Oz.	20

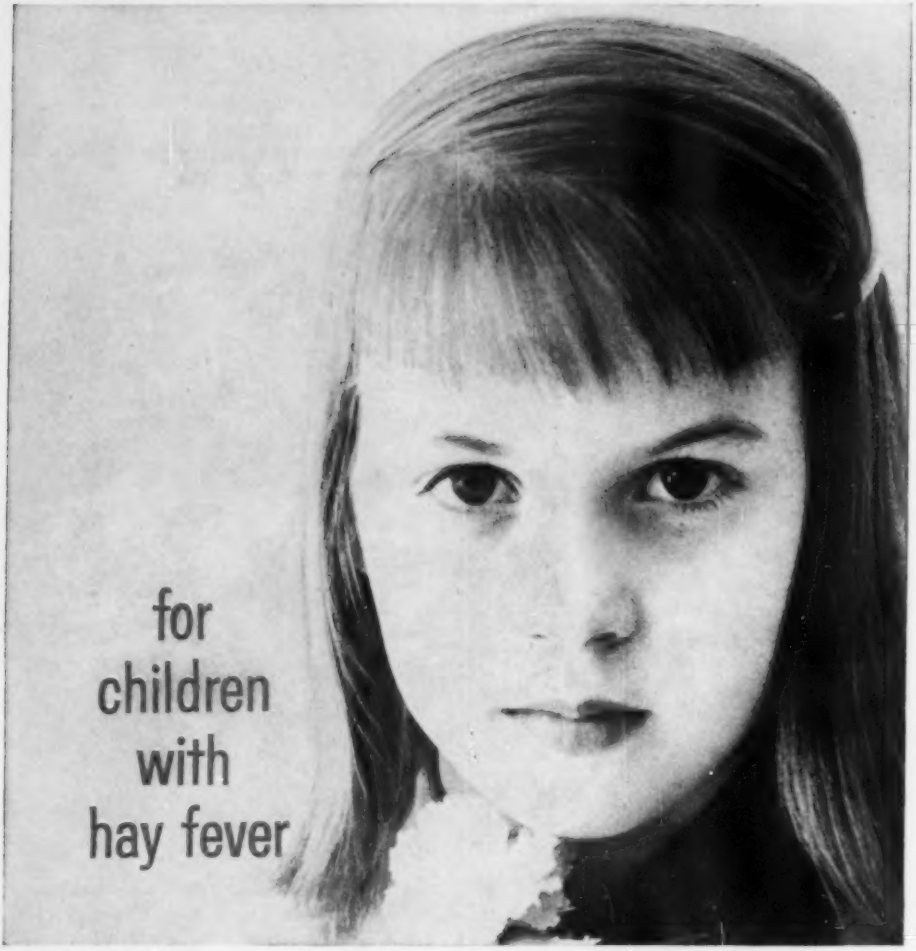
Increase caloric value as desired by the addition of a carbohydrate.

FULL-SIZE TRIAL CAN AVAILABLE ON REQUEST

Powdered in 14 oz. cans, Evaporated in 14 fl. oz. cans.

JACKSON-MITCHELL *Pharmaceuticals, Inc.*

10401-A Virginia Avenue, Culver City, Calif.



Novahistine works better than antihistamines alone

Stuffy, runny noses...swollen, weepy eyes are more effectively relieved with Novahistine. The distinctly additive action of the vasoconstrictor and antihistamine combined in Novahistine relieves allergic symptoms more effectively than either drug alone.

Each 5 cc. teaspoonful contains Phenylephrine hydrochloride 5.0 mg., Prophenpyridamine maleate 12.5 mg., Chloroform (approx.) 13.5 mg., l-Menthol 1.0 mg. and Alcohol 5%.

Dosage: Children—1 teaspoonful, 3 or 4 times daily Infants—¼ to ½ teaspoonful. Bottles of 4 and 16 oz.

PITMAN-MOORE COMPANY · Div. of Allied Laboratories, Inc., Indpls. 6, Ind.

Novahistine® Elixir

A.M.A JOURNAL OF
DISEASES OF CHILDREN

Studies on the Genetic Mechanism of Cystic Fibrosis of the Pancreas

MARVIN SMOLLER, M.D., and DAVID YI-YUNG HSIA, M.D., Chicago

Cystic fibrosis, a generalized disease of exocrine glands, manifests itself clinically by loss or diminution of pancreatic exocrine secretions, by increased susceptibility to upper respiratory infections, and pneumonia resulting in the pathologic changes of bronchiectasis, atelectasis, and emphysema, and by elevations of sodium and chloride concentrations in sweat gland secretions. In addition to the major manifestations, there is evidence pointing to an increase in salivary sodium and chloride concentrations, and abnormal duodenal mucosal gland secretions.

The familial nature of cystic fibrosis was first described by Andersen and Hodges [1] in 1946. A few years later, Lowe, May, and Reed,[2] using their own family data, and Carter,[3] analyzing the previously reported cases as well as his own, concluded that the inheritance pattern could best be explained on the basis of an autosomal recessive gene. More recently, Steinberg and his co-workers [4,5] have attempted to establish a possible linkage between cystic fibrosis and the blood groups. In the same study, they tested their family data by Weinberg's sib method and found them to be in good agreement with the single autosomal gene theory. The incidence of the disease was computed by Goodman and Reed [6] as 0.7-1.0 per 1,000 live births. They offered either a high mutation rate or superiority of the heterozygote as an explanation for the high incidence of an apparently lethal gene. The only family investigations reported are those by di Sant'Agnese and his co-workers[7] and by Shwachman and his co-workers.[11] The former performed sweat electrolyte tests on 18 families having affected children and found that 14 out of 60 parents and unaffected siblings had elevated sodium and chloride concentrations in their sweat.

During recent years, careful studies have shown wide variability in the clinical manifestations of this disease. Furthermore, sweat electrolyte abnormalities have been found in patients with chronic pulmonary disease [8,9] and in those with allergy.[10] Because of this, it appeared important to reinvestigate the possibility as to whether more than one gene could be operative and

TABLE 1.—*Daily Variation of Sweat Sodium Expressed as mEq/L in Four Normal Control Subjects*

Subject No.	No. of Determinations	Mean	S. E.
1	5	25.3	±4.2
2	6	16.5	±1.9
3	6	34.9	±4.0
4	3	25.2	±2.6

Submitted for publication Feb. 27, 1959.

These studies were aided by a grant from the National Cystic Fibrosis Research Foundation.

From the Genetic Clinic of The Children's Memorial Hospital; and the Department of Pediatrics, Northwestern University School of Medicine.

TABLE 2.—*Complete History of Thirty-Eight Families Having Children with Cystic Fibrosis*

	No.	Sex	Year of Birth	Living or Dead	Examined or Not	Wt. of Sweat, Mg.	Sweat Electrolytes, mEq/L		Duodenal Enzymes		Stool Trypsin Digests Gelatin in Dilution	Respiratory Status	Allergy History	Meconium Ileus
							Na	Cl	Amylase Gm. Glucose Liberated per 100 Cc.	Trypsin Gm. N Liberated per 100 Cc.				
A. Group 1. Complete Involvement														
1	M		1928	L	e	455.7	90.5	59.3	--	--	1-100	0	+	
	F		1928	L	e	651.5	55.2	47.6	--	--	1-200	0	0	
	AS$_1$	F	1955	L	e	721.2	140.0	102.0	--	--	No dig.	++	0	
2	M		1921	L	e	947.6	34.5	20.7	--	--	1- 10	0	0	
	F		1919	L	e	613.0	110.0	92.3	--	--	1- 10	0	0	
	S$_1$	M	1947	L	e	839.5	20.0	11.5	--	--	1-200	0	0	
	S$_2$	F	1949	L	e	651.2	50.8	36.9	--	--	1- 10	0	0	
	AS$_2$	M	1954	L	e	620.2	129.0	130.5	0	0.1	--	++	0	
3	M		1931	L	e	310.0	113.0	85.0	--	--	1- 10	+	0	
	F		1931	L	e	1,165.8	40.6	31.7	--	--	1- 10	0	0	
	AS$_1$	M	1954-57	D	ne	--	117.0	116.0	--	0	No dig.	++	0	
4	M		1926	L	e	912.5	16.8	12.8	--	--	1-200	0	0	
	F		1925	L	e	621.8	48.3	55.2	--	--	1-500	0	0	
	AS$_1$	M	1954	L	e	1,306.2	107.0	99.0	1.0	0.4	No dig.	++	0	
	S$_2$	F	1958	L	e	1,095.4	14.6	10.7	--	--	1-200	0	0	
5	M		1924	L	e	422.2	45.0	26.8	--	--	1-200	0	+	
	F		1925	L	e	433.8	67.0	34.6	--	--	1- 10	0	0	
	S$_1$	F	1950	L	e	564.7	47.0	29.5	--	--	1- 50	0	+	
	AS$_2$	F	1955	L	e	644.0	163.0	138.0	0.7	0	No dig.	++	0	
6	M		1920	L	e	558.6	66.0	45.3	--	--	1-200	+	++	
	F		1918	L	e	716.7	47.2	35.8	--	--	1- 10	0	0	
	S$_2$	M	1945	L	e	616.1	47.7	32.4	--	--	1-200	0	0	
	S$_2$	M	1951	L	e	535.0	96.0	76.7	--	--	1-200	0	++	
	AS$_2$	M	1955	L	e	702.8	172.5	141.0	0	0	--	++	0	
7	M		1922	L	e	757.8	50.9	37.0	--	--	1-500	0	0	
	F		1915	L	e	487.3	57.5	37.6	--	--	1-200	++	0	
	S$_1$	M	1946	L	e	943.4	20.2	17.0	--	--	1- 10	0	0	
	AS$_2$	F	1951-56	D*	ne	--	--	--	0	0	--	++	0	
	S$_2$	F	1954	L	e	778.2	36.6	30.1	--	--	1-200	0	0	
8	M		1931	L	e	861.2	45.0	30.2	--	--	1- 50	0	0	
	F		1931	L	e	1,169.1	16.6	9.4	--	--	1-200	0	0	
	AS$_1$	M	1956	L	e	667.1	138.0	117.0	0.5	0.6	--	++	0	
	S$_2$	M	1957	L	e	510.6	21.1	9.8	--	--	1- 10	0	0	
9	M		1928	L	e	473.4	72.0	49.4	--	--	1- 10	0	0	
	F		1929	L	e	381.1	26.3	28.0	--	--	1- 50	0	0	
	S$_1$	F	1946	L	e	731.1	75.5	55.0	--	--	1- 10	0	0	
	S$_2$	F	1951	L	e	867.9	32.0	20.5	--	--	1- 10	0	0	
	AS$_2$	M	1957	L	e	880.7	159.0	153.2	0	0	--	++	0	

10	M		1928	L	e	729.2	58.4	44.7	--	--	1- 10	0	0	
	F		1926	L	e	303.9	49.4	40.7	--	--	1- 5	0	0	
	S$_1$	F	1951	L	e	713.9	43.0	29.0	--	--	1-100	0	0	
	AS$_2$	M	1955	L	e	711.1	133.3	136.2	--	--	--	+	0	
11	M		1925	L	e	300.8	57.0	56.4	--	--	1-200	0	0	
	F		1923	L	e	905.7	58.0	23.8	--	--	1-500	0	0	
	S$_1$	M	1947	L	e	942.5	21.5	21.6	--	--	1-	0	0	
	S$_2$	M	1950	L	e	725.7	27.6	22.9	--	--	1-200	0	0	
	AS$_3$	M	1954-55	D *	ne	--	--	--	0	0	No dig.	++	0	
12	M		1926	L	e	566.1	32.3	15.9	--	--	1-100	0	0	
	F		1920	L	e	406.5	28.8	12.3	--	--	1- 5	0	0	
	S$_1$	F	1948	L	e	1,066.4	14.2	6.3	--	--	1-200	0	0	
	AS$_2$	F	1951-51	D *	ne	--	--	--	--	--	--	++	0	
	AS$_2$	F	1953-54	D	ne	--	--	--	11.5	0	--		0	
13	M		1911	L	e	229.7	91.5	114.0	--	--	1-500	0	0	
	F		1911	L	e	590.1	104.3	89.0	--	--	1-100	0	0	
	S$_1$	F	1934	L	e	186.6	56.4	55.4	--	--	1- 10	0	0	
	S$_2$	M	1937	L	e	522.9	30.4	49.8	--	--	1- 10	0	0	
	S$_3$	M	1949	L	e	342.2	74.5	64.3	--	--	1-500	0	0	
	AS$_4$	M	1953	L	e	1,189.9	149.0	148.0	0	0	No dig.	++	0	
14	M		1912	L	e	195.4	45.8	76.7	--	--	1- 10	0	0	
	F		1913	L	e	329.9	50.0	33.4	--	--	1- 5	+	0	
	AS$_1$	M	1944-44	D *	ne	--	--	--	--	--	--	++	0	
	AS$_2$	F	1948	L	e	891.3	87.0	87.7	0.4	0	--	++	0	
15	M		1921	L	e	397.7	67.9	40.2	--	--	1- 10	0	+	
	F		1917	L	e	684.9	27.0	32.8	--	--	1- 10	0	0	
	S$_1$	F	1950	L	e	528.5	62.0	51.6	--	--	1-100	0	0	
	AS$_1$	M	1953-56	D *	ne	?	65.0	83.0	--	--	No dig.	++	0	
	S$_2$	F	1955	L	e	513.3	30.2	31.1	--	--	1-200	0	0	
16	M		1910	L	e	378.1	17.8	12.3	--	--	1- 10	0	0	
	F		1907	L	e	2,841.1	60.8	56.4	--	--	1- 50	0	0	
	AS$_1$	F	1941-42	D	ne	--	--	--	--	--	--	++	0	
	S$_2$	F	1943	L	e	630.6	63.5	42.4	--	--	1-100	0	0	
	AS$_2$	M	1951			639.7	133.0	117.0	0	0.2	--	++	0	
B. Group 2. Meconium Ileus														
1	M		1920	L	e	726.0	97.0	44.8	--	--	1- 10	0	0	
	F		1909	L	e	1,499.8	76.0	53.5	--	--	1- 50	0	0	
	S$_1$	M	1950	L	e	863.0	8.9	7.0	--	--	1-100	0	0	
	AS$_2$	F	1954-54	D *	ne	--	--	--	--	--	--	++	0	+
2	M		1926	L	e	606.8	58.8	36.3	--	--	1- 10	0	+	
	F		1925	L	e	581.5	53.7	38.5	--	--	1- 50	0	0	
	AS$_1$	M	1948-48	D *	ne	--	--	--	--	--	--	+	0	+
	S$_2$	F	1950	L	e	476.5	44.9	32.2	--	--	1- 50	0	0	
	AS$_3$	M	1952	L	e	1,862.0	141.0	129.0	--	--	1-100	+	0	
	S$_4$	M	1954	L	e	3,277.0	72.5	66.1	--	--	1-200	0	0	
3	M		1918	L	e	428.2	40.8	35.8	--	--	1-100	0	0	
	F		1918	L	e	885.1	40.4	32.4	--	--	1- 50	0	0	
	AS$_1$	F	1947-47	D *	ne	--	--	--	--	--	--	?	0	

TABLE 2.—*Complete History of Thirty-Eight Families Having Children with Cystic Fibrosis*—Continued

	No.	Sex	Year of Birth	Living or Dead	Examined or Not	Wt. of Sweat, Mg.	Sweat Electrolytes, mEq/L		Duodenal Enzymes		Stool Trypsin Digests Gelatin in Dilution	Respiratory Status	Allergy History	Meconium Ileus
							Na	Cl	Amylase Gm. Glucose Liberated per 100 Cc.	Trypsin Gm. N Liberated per 100 Cc.				
	AS_1	F	1949	L	e	577.1	125.5	123.0	0	0.28	--	+	0	
	AS_2	F	1953	L	e	880.9	147.5	133.0	--	--	No dig.	+	0	+
4	M		1923	L	e	304.8	63.2	35.0	--	--	No dig.	0	0	
	F		1917	L	e	1,791.2	54.0	39.7	--	--	1- 50	0	0	
	AS_1	F	1948	L	e	862.4	129.0	114.0	0.1	0.2	--	+	0	
	S_2	F	1949	L	e	997.6	34.0	26.1	--	--	1- 50	0	0	
	AS_2	F	1951-51	D *	ne	--	--	--	--	--	--	++	0	+
5	M		1929	L	e	899.7	51.4	31.5	--	--	1-100	0	0	
	F		1924	L	e	1,000.6	45.0	38.0	--	--	1- 10	0	0	
	AS_1	M	1949	L	e	780.5	123.0	114.0	0.1	0.3	--	++	0	
	S_2	M	1952	L	e	2,187.4	28.6	17.5	--	--	1-100	0	0	
	AS_3	M	1953-53	D *	ne	--	--	--	--	--	--	++	0	+
6	M		1925	L	e	192.2	59.8	44.7	--	--	1- 50	0	0	
	F		1919	L	e	773.8	48.4	41.3	--	--	1- 10	0	0	
	S_1	F	1946	L	e	245.5	63.1	43.1	--	--	1-200	0	0	
	AS_2	M	1950	L	e	342.3	149.7	140.2	0.6	0	--	+	0	+
7	M		1927	L	e	361.9	91.5	49.8	--	--	1- 10	0	0	
	F		1924	L	e	702.2	134.5	88.0	--	--	1- 10	0	0	
	S_3	M	1947	L	e	632.1	33.6	33.8	--	--	1- 10	0	0	
	S_2	F	1949	L	e	926.3	17.8	14.4	--	--	1- 50	0	0	
	S_4	F	1955	L	e	780.3	31.0	43.6	--	--	1-200	0	0	
	AS_4	F	1956-56	D *	ne	--	--	--	--	--	--	++	0	+
8	M		1930	L	e	454.7	9.6	6.7	--	--	1-200	0	+	
	F		1928	L	e	977.5	52.5	37.2	--	--	1- 50	0	0	
	S_1	F	1952	L	e	919.4	24.3	18.5	--	--	1-100	0	0	
	S_2	M	1954	L	e	618.9	56.6	47.8	--	--	1-100	0	0	
	AS_3	M	1954-54	D *	ne	--	--	--	--	--	--	++	0	+
9	M		1926	L	e	853.4	17.9	9.0	--	--	1-100	0	+	
	F		1924	L	e	384.1	46.9	39.0	--	--	1- 10	0	0	
	S_1	F	1950	L	e	1,281.8	34.2	26.9	--	--	1-200	0	0	
	AS_2	M	1952-52	D	ne	--	--	--	0.29	0	--	+	0	+
	S_2	F	1954	L	e	1,572.2	59.0	51.5	--	--	1-100	0	0	
10	M		1924	L	e	1,313.8	64.7	48.0	--	--	1- 10	0	0	
	F		1926	L	e	769.1	29.3	17.4	--	--	1- 10	0	0	
	S_1	M	1952	L	e	571.3	48.1	41.4	--	--	1-200	0	0	
	S_2	F	1953	L	e	411.8	45.0	33.2	--	--	1-500	0	0	
	AS_3	M	1955	L	e	1,031.0	152.5	143.5	2.1	0.3	No dig.	++	0	
	AS_4	M	1956	L	e	473.3	144.0	128.0	--	--	No dig.	+	0	+
	S_4	M	1958	L	e	792.2	18.0	19.4	--	--	1-200	0	0	
11	M		1931	L	e	393.8	40.7	24.5	--	--	1- 10	0	0	
	F		1928	L	e	177.3	48.0	29.9	--	--	1-200	0	0	

	AS_1	F	1952	L	e	1,735.0	101.0	100.2	0	0.07	--	0	0	
	AS_2	M	1953-55	D*	ne	--	--	--	--	--	No dig.	++	0	+
12	M		1929	L	e	166.3	46.6	26.0	--	--	1- 50	0	0	
	F		1926	L	e	796.5	37.7	28.9	--	--	1- 10	0	0	
	S_1	M	1951	L	e	599.2	54.2	37.2	--	--	1-100	0	0	
	AS_2	F	1956-56	D*	ne	127.8	99.0	51.0	0.1	1.0	--	++	0	+
C. Group 3. Partial Involvement														
1	M		1927	L	e	424.1	57.2	30.6	--	--	1- 10	0	0	
	F		1925	L	e	298.9	71.2	50.2	--	--	1- 10	0	0	
	S_1	M	1949	L	e	280.4	28.9	11.7	--	--	1-100	0	0	
	S_2	M	1952	L	e	1,827.4	25.9	35.0	--	--	1-200	+	0	
	AS_2	M	1956	L	e	1,656.1	30.1	18.7	--	--	No dig.	++	0	
2	M		1922	L	e	644.2	27.0	13.4	--	--	1-200	0	0	
	F		1915	L	e	564.9	81.2	46.8	--	--	1-200	0	0	
	S_1	M	1953	L	e	549.6	24.6	19.4	--	--	1-100	0	0	
	AS_2	M	1956	L	e	(1) 699.6	28.0	23.4	0.9	0.4	1- 50	0	+	
						(2) 999.3	29.0	22.6						
3	M		1921	L	e	2,668.6	12.2	8.1	--	--	1-200	0	0	
	F		1915	L	e	422.5	13.8	4.7	--	--	1- 10	0	0	
	S_1	F	1943	L	e	1,100.6	19.5	16.3	--	--	1- 10	0	0	
	AS_2	F	1950	L	e	860.4	93.0	83.8	0	0.1	--	0	0	
	AS_2	M	1954	L	e	1,020.8	102.0	97.0	--	0	No dig.	++	0	
4	M		1915	L	e	373.1	31.8	25.7	--	--	1- 50	0	0	
	F		1915	L	e	618.5	79.5	64.4	--	--	1-500	0	+	
	S_1	F	1942	L	e	345.5	38.0	25.8	--	--	1-500	0	0	
	AS_1	M	1947	L	e	480.1	95.1	86.4	6.0	0.05	--	++	0	
	AS_1	M	1947	L	e	354.4	106.0	100.5	5.03	0.2	--	++	0	
5	M		1921	L	e	487.1	35.7	27.4	--	--	1- 10	0	0	
	F		1919	L	e	312.2	168.0	141.0	--	--	1-500	++	0	
	S_1	F	1942	L	e	352.9	57.7	37.8	--	--	1- 10	0	0	
	AS_2	F	1943	L	e	351.9	94.2	91.2	--	12.1	1-500	++	0	
6	M		1934	L	e	158.2	78.3	67.0	--	--	1-200	0	0	
	F		1928	L	e	835.4	44.0	29.4	--	--	1-200	0	0	
	AS_2	F	1956	L	e	247.1	71.8	58.8	0.4	3.6	1- 50	0	0	
D. Group 4. Long Survivors														
1	M		1920	L	e	856.0	59.0	31.4	--	--	1- 10	0	0	
	F		1922	L	e	801.4	71.7	63.0	--	--	1- 50	0	0	
	S_1	F	1942	L	e	388.0	41.0	37.0	--	--	1- 10	0	0	
	AS_2	M	1947	L	e	747.3	101.2	85.5	--	--	No dig.	++	0	
	S_2	F	1949	L	e	1,137.8	51.8	37.4	--	--	1-100	?+	0	
2	M		1915	L	e	264.3	70.0	53.0	--	--	1-500	0	0	
	F		1905	L	e	2,036.5	63.3	54.6	--	--	1- 5	0	0	
	AS_1	M	1948	L	e	519.8	159.0	142.0	0	0	--	++	0	
	AS_2	F	1952-56	D*	ne	437.5	142.0	140.0	0	0	--	++	0	
3	M		1916	L	e	237.5	39.4	18.1	--	--	1-100	0	0	
	F		1909	L	e	300.2	61.7	55.4	--	--	1- 10	0	0	
	AS_1	F	1942	L	e	200.5	128.0	128.3	--	--	1- 5	0	+	
	AS_2	M	1943-57	D	ne	--	--	--	--	--	--	++	0	

TABLE 2.—*Complete History of Thirty-Eight Families Having Children with Cystic Fibrosis*—Continued

	No.	Sex	Year of Birth	Living or Dead	Examined or Not	Wt. of Sweat, Mg.	Sweat Electrolytes, mEq/L		Duodenal Enzymes		Stool Trypsin Digests Gelatin in Dilution	Respiratory Status	Allergy History	Meconium Ileus
							Na	Cl	Amylase Gm. Glucose Liberated per 100 Cc.	Trypsin Gm. N Liberated per 100 Cc.				
	S_2	M	1946	L	e	739.9	86.8	80.0	--	--	1- 50	0	0	
	AS_4	M	1947	L	e	386.0	125.0	107.0	--	--	No dig.	+	0	
	AS_3	F	1952-54	D [a]	ne	--	--	--	0	0	--	++	0	
	S_3	M	1954	L	e	308.5	43.1	34.4	--	--	1-500	0	0	
4	M		1919	L	e	479.1	24.5	15.2	--	--	1- 10	0	0	
	F		1918	L	e	753.4	10.2	7.6	--	--	1- 50	+	0	
	AS_2	M	1944	L	e	567.0	143.5	122.0	0.07	0.132	No dig.	++	0	
	S_2	F	1946	L	e	769.5	24.7	12.5	--	--	1- 10	0	0	
	S_3	F	1949	L	e	714.8	30.8	23.8	--	--	1- 10	0	0	
	S_4	M	1952	L	e	754.9	38.4	26.6	--	--	1- 50	0	0	

[a] Postmortem confirmation of cystic fibrosis.

M = mother; F = father; S_1 = first sib; AS_1 = first sib affected with cystic fibrosis.

Respiratory status: 0 = (*a*) no history of chronic lung disease; (*b*) normal chest x-ray; + = (*a*) history of chronic lung disease; (*b*) normal chest x-ray; ++ = (*a*) history of chronic lung disease; (*b*) abnormal chest x-ray.

Allergic history: 0 = no allergies; + = minor allergies; ++ = major allergies — hay fever, asthma.

to ascertain if clinically well heterozygous carriers could be detected.

Materials and Methods

In order to demonstrate maximum differences between families, the following four groups were selected: (1) 16 families who had children with complete involvement typically seen in cystic fibrosis of the pancreas; (2) 12 families where at least one child had meconium ileus; (3) 6 families where at least one child had only partial involvement (this included those with some duodenal enzyme activity, those with no previous history of pulmonary disease, or those with normal sweat electrolyte concentrations); (4) 4 families where at least one affected child with the typical clinical picture of cystic fibrosis had survived to the age of 8 years or older.

The controls consisted of normal healthy parents and siblings of children seen in the well baby clinic. All of the controls were free of pulmonary disease and allergy, and were not on steroid therapy.

Sweat electrolyte tests were performed on each member of the family (parents, affected children, and unaffected children) according to a modification of the method described by Schwachman and his co-workers.[11] A weighed electrolyte-free gauze square was placed on a washed section of the lower back and covered with a larger clean plastic square, which was taped to the skin. The subject was then wrapped with plastic around the waist, and an electric heating pad was applied to the back to stimulate sweating. The gauze square was removed after approximately 60 minutes, reweighed and analyzed for sodium in a flame photometer and for chloride by titration by the method of Wilson and Ball,[12] as modified by Kramer.[13]

All sweat tests on both controls and experimental families were carried out by the same physician in the same room, under the same conditions and at the same time of the year—June, July, and August. Each subject produced sweat samples at his or her own rate under similar experimental conditions, and the weights of these samples were recorded. The degree of variability of electrolyte content in day-to-day sweat collections was studied in a number of normal controls (Table 1). It would appear that this factor was insufficient to lead to misclassification.

The respiratory status was assessed by history and a chest x-ray. A patient having repeated upper respiratory infections together with more than two episodes of pneumonia was classified as having a positive pulmonary history (+). If in addition the chest x-ray was abnormal, the patient was put into a second group (++).

The pancreatic enzyme secretions were evaluated in most of the affected children by duodenal intubation and analysis of the secretions for amylase and trypsin activity by the method of Free and Myers.[14] On the basis of these tests and history, the affected children were divided into three groups: (1) those with subnormal duodenal enzyme activity; (2) those with no duodenal enzyme activity; (3) those with meconium ileus. Because of technical problems, the only evaluation of parents' and unaffected siblings' duodenal enzyme activity was by testing various dilutions of their stools for the ability to digest gelatin.

An allergic history was also taken. The patients having urticaria, eczema, and food allergies were placed in Group 1 (+) and those having hay fever and asthma in Group 2 (++).

Results

The complete family data are presented in Table 2.

1. *Comparison of Sweat Electrolyte Concentrations.*—In Figures 1A and 1B the sweat sodium and chloride concentrations of normal controls, affected children, parents of affected children, and siblings of affected children are compared. It can be seen that the affected children are at one end of the scale and the controls at the other with minimal overlap. The parents lie between the two extreme groups with a great deal of overlap, but approximately 50% of the parents have higher sweat sodium concentrations than 95% of the controls. The unaffected siblings lie between their parents and the controls with a great deal of overlap in both directions. A similar, though not quite as striking, difference was noted with sweat chlorides. The means, standard errors, and ranges of each group are given in Table 3. The differences between the means of the four groups are highly significant ($P=0.01$).

2. *Tests for Recessive Mode of Inheritance.*—In Table 4 the data have been tested according to the a priori method.[15] The difference between the total expected and observed affected children is less than 2 standard deviations and is therefore, not significant.

Another method was used to determine whether this disease is due to a recessive gene. In such a disease all the parents and

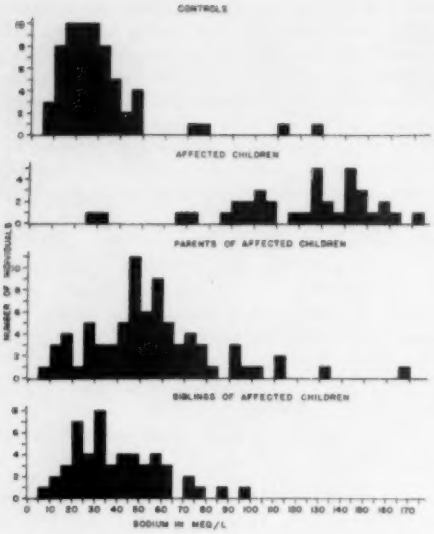


Figure 1A

Fig. 1A.—A comparison of sweat sodium (expressed as mEq/L) in normal controls, affected children, parents of affected children, and siblings of affected children.

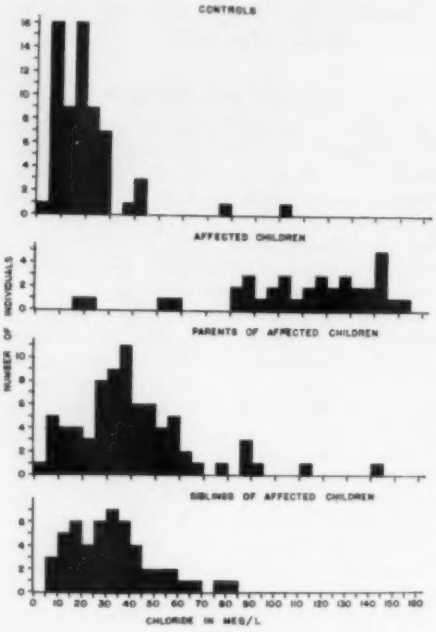


Figure 1B

Fig. 1B.—A comparison of sweat chloride (expressed as MEq/L) in normal controls, affected children, parents of affected children, and siblings of affected children.

TABLE 3.—*Sweat Sodium and Chloride (Expressed as MEq/L) in Normal Controls, Affected Children, Parents of Affected Children, and Siblings of Affected Children*

	No.	Mean	S. E.	Range	Mean	S. E.	Range
I. Normal Controls							
A. Adults							
1. Males	16	29.1	±3.7	8.0- 74.4	18.8	±2.5	6.1-44.8
2. Females	18	34.0	±5.2	12.4-113.0	18.7	±2.9	7.6-76.3
3. All	34	32.0	±3.0	8.0-113.0	18.7	±2.2	6.1-76.3
B.							
1. Males	20	26.9	±6.3	7.6-126.0	20.6	±4.9	3.1-101.0
2. Females	10	30.5	±3.5	10.2- 47.6	21.1	±3.2	7.0- 38.0
3. All	30	28.1	±4.4	7.6-126.0	20.8	±3.4	3.1-101.0
C. All controls	64	30.2	±2.6	7.6-126.0	19.8	±1.9	3.1-101.0
II. Children with Cystic Fibrosis							
1. Males	24	121.0	±7.6	28.0-172.0	111.6	±7.1	18.7-153.0
2. Females	13	116.0	±7.7	71.0-163.0	103.9	±8.1	51.0-140.0
3. All	37	119.5	±5.5	28.0-172.0	109.0	±5.4	18.7-153.0
III. Parents of Children with Cystic Fibrosis							
1. Males	38	57.3	±5.1	10.2-168.0	43.7	±5.1	4.7-141.0
2. Females	38	52.1	±3.9	9.6-113.0	37.1	±3.7	6.7-114.0
3. All	76	54.7	±2.8	9.6-168.0	40.6	±2.8	4.7-141.0
IV. Siblings of Children with Cystic Fibrosis							
1. Males	23	40.4	±4.9	8.9- 96.0	34.1	±4.5	7.0- 80.0
2. Females	28	40.8	±3.1	14.2- 75.5	31.3	±2.5	6.3- 55.4
3. All	51	40.6	±2.8	8.9- 96.0	32.6	±2.4	6.3- 80.0

TABLE 4.—*A Priori Test for Recessive Mode of Inheritance*

Family Size	No. of Families	No. of Affected Observed	No. of Affected Expected	Variance
2	12	15	12.713	1.464
3	17	25	22.054	4.471
4	4	5	5.851	1.080
5	1	2	1.038	.592
6	1	4	1.824	.776
Total	35	51	45.080	8.983

* The difference between the observed and expected = 5.920 or 1.978 S. D.

two-thirds of the unaffected siblings should be heterozygotes, and it can be expected, therefore, that the mean unaffected sib sweat sodium and chloride should equal the average of twice the mean parent values plus the mean control values ($S=\frac{2p+c}{3}$). The concentrations observed can then be compared to the calculated values of S to determine whether both represent the same population. The expected sodium value is 46.5±2.7 mEq/L and the observed 40.6±2.8 mEq/L. Similarly, the expected chloride mean is 33.7±2.5 mEq/L and observed 32.6±2.4 mEq/L. These differences are not statistically significant.

3. *Sex Segregation.*—The sex distribution of affected children is 32 males to 22 females (Table 5). On application of the χ^2 test, the difference between observed and expected is not significant and can be attributed to sampling error. Also, no significant difference was noted between the mean sweat electrolyte concentrations of males and females in the control group or in the three affected family groups (Table 3).

TABLE 5.—*Sex Distribution Among Children Affected with Cystic Fibrosis*

	Observed	Expected
Males	32	27
Females	22	27

* χ^2=1.8518. D. F. =1. P=0.10—0.20.

4. *Comparison of Affected Siblings.*—To determine whether all the affected children in a family had the same clinical manifestations, the degree of involvement of one child was plotted against that of his affected siblings (Tables 6A and 6B). It is suggestive from the tables that children of the same family often have similar degrees of pancreatic exocrine and pulmonary involvement. The sweat electrolyte concentrations of only six sib pairs were available for comparison since many had died prior to the routine use of the test. Although Figure 2 shows a positive correlation in these six sib pairs for both sweat sodium ($R=+0.869$; P 0.01-0.02) and sweat chloride ($R=+0.836$; P 0.02-0.05), this observation remains to be confirmed on a larger sample.

TABLE 6A.—*Correlation of Duodenal Enzyme Involvement in Affected Sibling Pairs*

Affected Sibling \ Proband	0	1	2	3
3		1		
2		4	10	3
1		1		
0				

Numbers in squares represent sibling pairs. 0=normal duodenal enzymes; 1=partially deficient duodenal enzymes; 2=completely deficient duodenal enzymes; 3=meconium ileus.

TABLE 6B.—*Correlation of Pulmonary Involvement in Affected Sibling Pairs*

Affected Sibling \ Proband	0	1	2
2		2	6
1		2	2
0		1	4

0=no pulmonary symptoms; 1=pulmonary symptoms with a normal chest x-ray; 2=pulmonary symptoms with an abnormal chest x-ray.

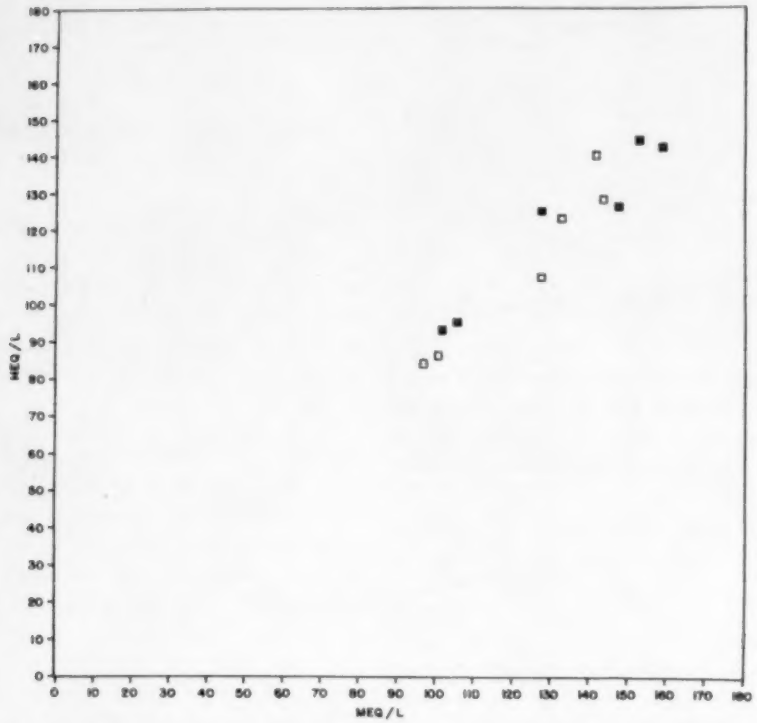


Fig. 2.—The sib-sib correlation of sweat sodium, shown in solid squares, and the sweat chloride, shown in open squares. Both are expressed as mEq/L. (Correlation coefficient for Na (r)=+0.869; d. f. =5, P=<0.02. Correlation coefficient for Cl (r)=+0.836; d. f. =5, P=<0.05.

5. *Relation of Parents' and Affected Children's Sweat Sodium.*—The affected children's sweat sodium levels were plotted against those of their parents (Fig. 3); the correlation coefficient indicates no apparent relationship (R=0.021, P=0.80-0.90). There was also no correlation between the mean sweat sodium values of both parents and their affected children. The final family study showed that the distribution of parents with elevated sweat electrolyte concentration was random. In some families both parents had high values, in others both had low, and in the rest one had high values and the other low.

6. *Relation of Sweat Involvement to Pancreatic and Pulmonary Involvement.*—The sweat sodium concentrations of affected children were compared with their duodenal enzyme and pulmonary status in Tables 7A and 7B. It can be noted from this study that although sweat electrolyte values in the range of 100-150 mEq/L are most often associated with complete loss of pancreatic enzyme activity and severe pulmonary disease, concentrations above 150 mEq/L are not related to meconium ileus and concentrations below 100 mEq/L are not consistently associated with milder pancreatic and pulmonary involvement.

7. *Relation of Sweat Sodium to Chloride.* Figure 5 indicates that the sweat sodium and chloride are directly related (correlation coefficient = R+0.691, P less than 0.01), and, as seen in Figure 5, the sodium concentration is almost always greater than the chloride. In Figure 6 it can be noted that the high sodium values have a sodium/chlo-

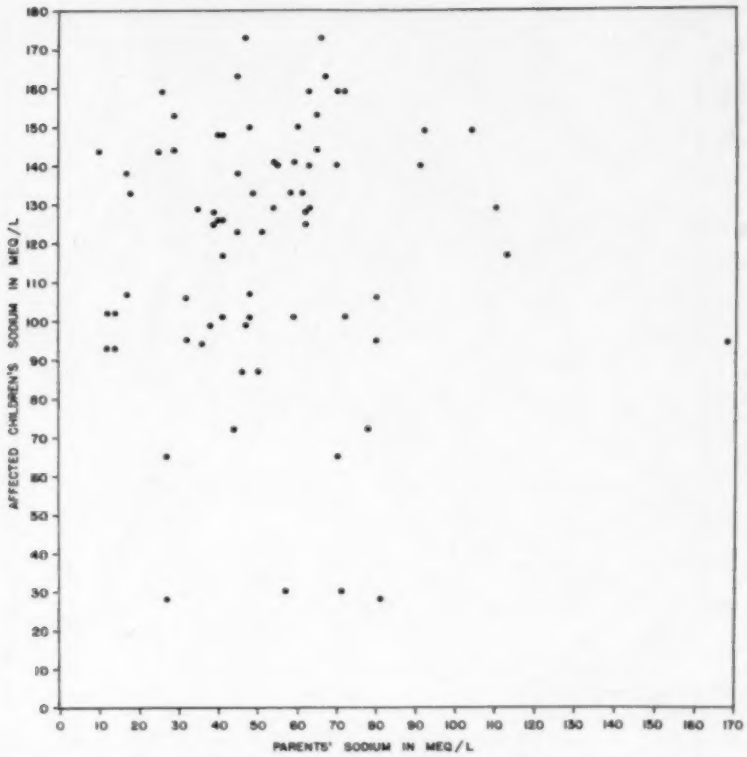


Fig. 3.—The sweat sodium of parents of affected children as plotted against their affected childrens' sweat sodium (expressed as mEq/L). (Correlation coefficient (r)=+.021; d. f.=73; P=0.80—0.90.)

ride ratio close to one, but most of the lower values have a Na/Cl ratio greater than one.

8. *Stool and Respiratory Studies.*—The stool samples of affected children's parents and siblings did not differ in trypsin activity from samples obtained from normal adults and children (Table 8). Either the test is of no apparent value in detecting subtle differences in duodenal enzyme activity or no difference exists.

The respiratory studies revealed three parents that had a positive history and an abnormal chest x-ray. One unaffected sibling had a positive history and one had an abnormal chest x-ray but no history of pulmonary disease.

Comment

In a recent publication, Childs [16] has shown that upon statistical analysis, cystic fibrosis is transmitted as an autosomal recessive gene. However, he points out the possibility that the variable clinical picture may be caused by a system of alleles at one locus, or even of several genes at different loci, which result in full expression of the disease in homozygotes, but in only partial expression in some heterozygotes. Although the number of families in our study is small, there appears to be some similarity in the degree of involvement within the same family in terms of both duodenal enzymes and pulmonary disease. One would not expect perfect segregation when the techniques for classification are relatively crude and arbitrary. Furthermore, the difference may be due in part to the age of the affected child, with the degree of both duodenal and pulmonary involvement

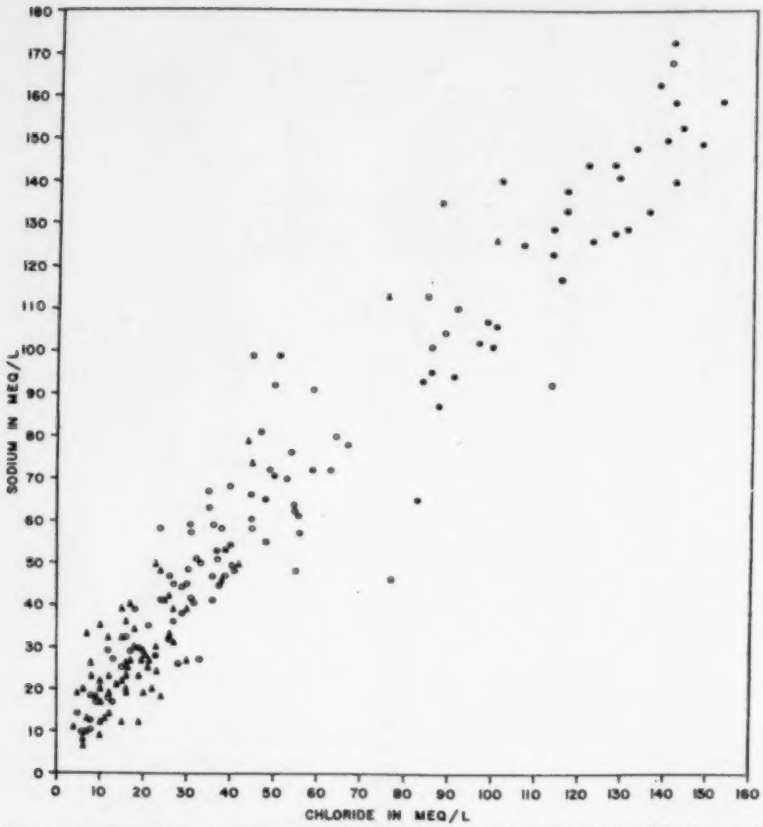


Fig. 4.—A comparison of sodium and chloride (expressed in mEq/L) in 177 persons. The affected persons are represented by solid circles, the parents of affected children by open circles, and the normal controls by triangles. (Correlation coefficient (r)=+.691; degrees of freedom=176; $P=<.01$.)

TABLE 7A.—*Correlation of Affected Childrens' Sweat Electrolytes Sodium vs. Duodenal Enzyme Status*

Duodenal Enzymes	Sodium 0	Sodium 1	Sodium 2	Sodium 3
3		1	1	
2	1	3	19	5
1	1	3	3	
0				

Sodium: 0=0-50 MEq/L; 1=50-100 MEq/L; 2=100-150 MEq/L; 3=150-200 MEq/L

Duodenal enzymes: 0=normal enzymes; 1=low enzyme activity; 2=absent enzymes; 3=meconium ileus

TABLE 7B.—*Correlation of Affected Childrens' Sweat Electrolyte Sodium vs. Pulmonary Status*

Pulmonary Status	Sodium 0	Sodium 1	Sodium 2	Sodium 3
2	1	5	13	5
1			8	
0	1	2	2	

Sodium: 0=0-50 MEq/L; 1=50-100 MEq/L; 2=100-150 MEq/L; 3=150-200 MEq/L.

Pulmonary status: 0=normal; 1=pulmonary symptoms with normal chest x-ray; 2=pulmonary symptoms with abnormal chest x-ray.

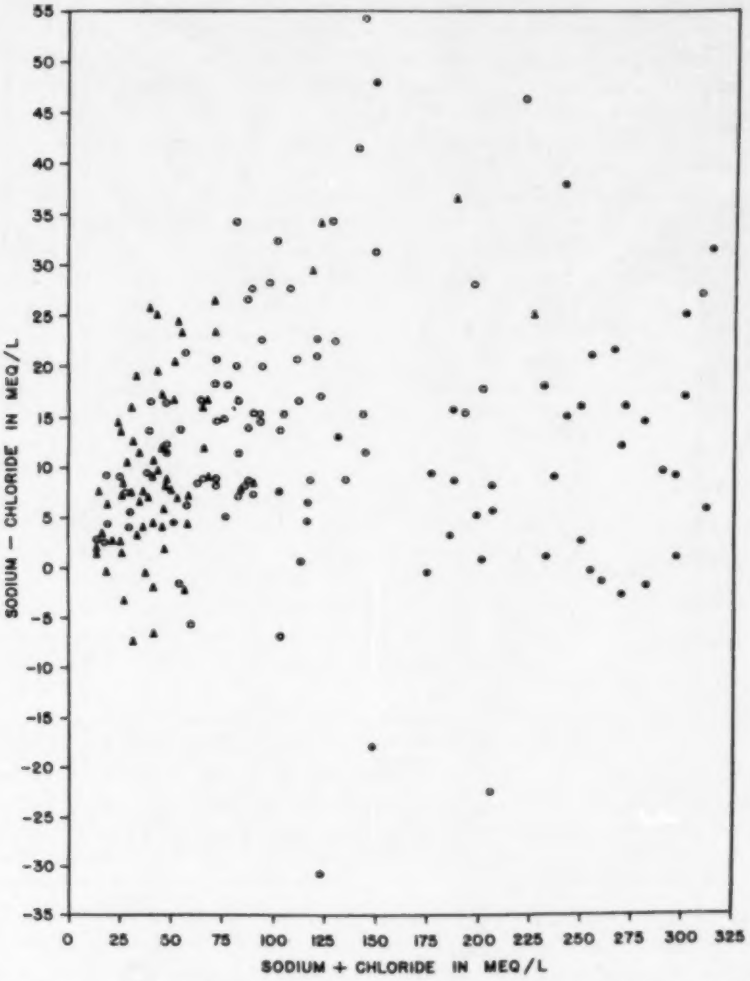


Fig. 5.—The sweat Na—Cl as plotted against the Na+Cl (both expressed as mEq/L). The affected children are represented by solid circles, the parents of affected children by open circles, and the normal controls by triangles.

increasing with age. Although a multiple gene system of some type fits well with some of the data, it should be remembered that a single gene could be modified in some individuals by other genes and by environmental factors to produce the variable clinical picture seen. Further studies of this type involving larger numbers of families may eventually help to clarify this point.

Since it has been demonstrated in many genetic diseases that heterozygotes have, to a slighter degree, the same biochemical abnormality as the homozygote, it was expected that all the parents and two-thirds of the unaffected siblings studied might have elevated sweat sodium and chloride concentrations.[17] However, in order to detect subtle differences between carriers of the disease and normal persons, it was nec-

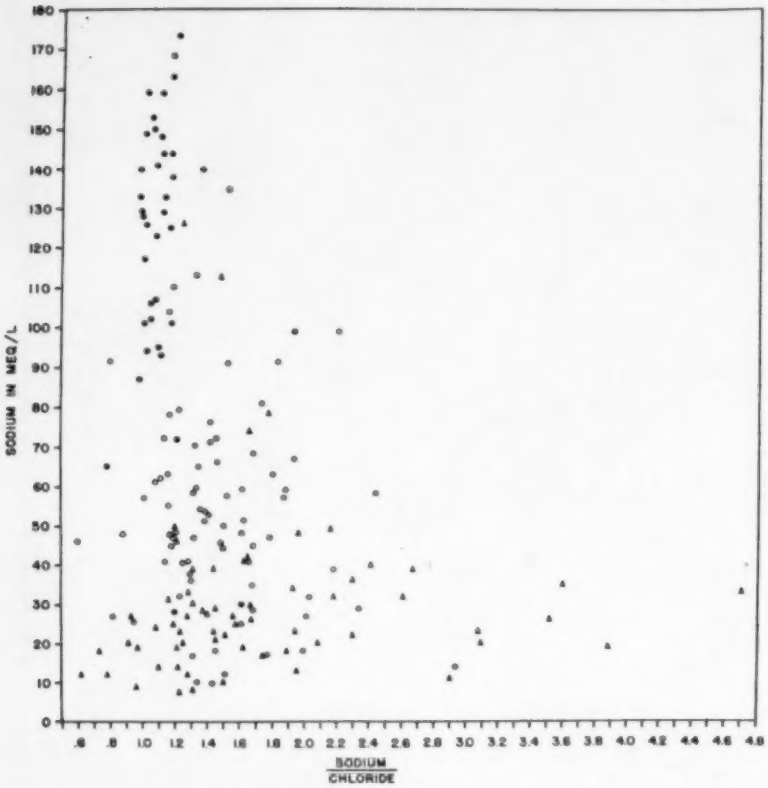


Fig. 6.—The sweat sodium (expressed as mEq/L) as plotted against the Na/Cl ratio. The affected individuals are represented by solid circles, the parents of affected children by open circles, and the normal controls by triangles. It can be noted that higher values of sodium tend to have a Na/Cl ratio of 1, and that the lower sodium values tend to have a Na/Cl ratio of considerably more than 1.

essary first to establish a restricted upper level below which most of the normal subjects fell. In our control group approximately 95% had a sweat sodium concentration of less than 50 mEq/L. One-half of the parents and one-third of the unaffected siblings studied had sweat sodium concentrations beyond this upper limit of normal and were, therefore, considered demonstrable heterozygotes. It is conceivable that under appropriate stress (as applied in determining the carrier of phenylketonuria),[18] the remaining half of the parents and one-third of the unaffected siblings could be found to differ in some respect from the control group. To date the proper stress has not been found. The fact that some heterozygotes are detectable in cystic fibrosis lends weight to the theory that even a so-called recessive gene has some expression in the heterozygous state.[17]

When the relationship of the sodium to chloride concentration in the sweat of af-

TABLE 8.—*Stool Trypsin Values in Normal Controls*

Stool Dilutions	No. Child.	No. Adults
No dig.	0	0
1-5	0	4
1-10	3	4
1-50	5	6
1-100	3	2
1-200	5	3
1-500	4	1

fected children, their parents and normal controls was analyzed, it was found that the concentrations of the two ions are directly related and that the sodium is usually higher than the chloride (Figs. 3 and 4). This relationship appears to be one of the most consistent findings in sweat gland secretions.[19-21] When the Na/Cl ratio was plotted against the sodium concentration (Fig. 5) a possible difference was noted between the affected children and the controls. The affected children had an average Na/Cl ratio of 1.12 with minimal scatter about this line, whereas the controls had an average ratio of 1.73 with wide scatter. On investigation of the Na/Cl values of the two groups a possible explanation of the Na/Cl ratio differences became evident. It was noted that both groups had similar average differences between their sweat sodium and chloride concentration (Na/Cl in controls =10.5 mEq/L; in affected children 10.6 mEq/L), and therefore the increased concentrations of both sweat sodium and chloride of the affected children would give them a lower Na/Cl ratio than the controls. If it is postulated that the difference between sodium and chloride represents the concentration of sweat anions other than chloride ions, then the possible significance of these observations lies in their confirmation of other investigators' conclusions that the concentration of these substances is not increased in the sweat of children with cystic fibrosis.[8,22]

Summary and Conclusions

Complete family studies have been undertaken in 38 families having children with cystic fibrosis of the pancreas. It was found that sweat sodium levels were above normal limits in about half of the parents. A similar increase was noted in one-third of the normal siblings.

The data demonstrated some segregation of clinical symptoms and laboratory findings within families. However, on the limited number of families studied, one could not rule out the possibility that the variable clinical picture seen in cystic fibrosis could be the result of a single gene being modified by other genes and by environmental factors.

The relationship of sodium to chloride concentration in sweat gland secretions was analyzed and discussed.

The authors wish to express their appreciation to Dr. H. Harris for assistance in analyzing the data.

707 Fullerton Ave. (14) (Dr. Hsia).

REFERENCES

1. Andersen, D. H., and Hodges, R. G.: Celiac Syndrome: V. Genetics of Cystic Fibrosis of the Pancreas with a Consideration of Etiology, Am. J. Dis. Child. 72:62, 1946.

2. Lowe, C. U.; May, C. D., and Reed, S. C.: Fibrosis of the Pancreas in Infants and Children, Am. J. Dis. Child. 78:349, 1949.

3. Carter, C. O., in Fibrocystic Disease of the Pancreas, edited by M. Bodian, New York, Grune & Stratton, Inc., 1953, p. 50-64.

4. Steinberg, A. G.; Shwachman, H.; Allen, F. H., Jr., and Dooley, R. R.: Linkage Studies with Cystic Fibrosis of the Pancreas, Am. J. Human Genet. 8:162, 1956.

5. Steinberg, A. G., and Morton, N. E.: Sequential Test for Linkage Between Cystic Fibrosis of the Pancreas and the MNS Locus, Am. J. Human Genet. 8:177, 1956.

6. Goodman, H. O., and Reed, S. C.: Heredity of Fibrosis of the Pancreas: Possible Mutation Rate of the Gene, Am. J. Human Genet. 4:59, 1952.

7. di Sant'Agnese, P. A.; Darling, R. C.; Perera, G. A., and Shea, E.: Sweat Electrolyte Disturbances Associated with Childhood Pancreatic Disease, Am. J. Med. 15:777, 1953.

8. Weeks, M. M., and Brown, G. A.: Sweat Analysis in Fibrocystic Disease, Chronic Pulmonary Disease, and Controls, Arch. Dis. Childhood 33:74, 1958.

9. Hugh-Jones, D., and Hsia, D. Y.-Y.: Unpublished observations.

10. Hsia, D. Y.-Y.; Driscoll, S. G.; Greenberg, D.; Lee, T.-C., and Lanoff, G.: Abnormality of Sweat Electrolytes in Patients with Allergies, A. M. A. J. Dis. Child. 96:685, 1958.

11. Shwachman, H.; Leubner, H., and Catzel, P.: Mucovisidosis, Advances Pediat. 7:249, 1955.

12. Wilson, D. W., and Ball, E. G.: A Study of the Estimation of Chloride in Blood and Serum, J. Biol. Chem. 79:221, 1928.

13. Kramer, B.: Inorganic Constituents, in Encyclopedia of Medicine, Surgery, and Specialties,

Philadelphia, F. A. Davis Company, 1944, Vol. 2, p. 594.

14. Free, A. H., and Myers, V. C.: Estimation of the Enzymes, Amylase, Proteinase and Lipase in Duodenal Contents, J. Lab. & Clin. Med. 28:1387, 1943.

15. Neel, J. V., and Schull, W. J.: Human Heredity, Chicago, University of Chicago Press, 1954, pp. 211-229.

16. Childs, B., in Fibrocystic Disease of the Pancreas: Report of 18th Ross Pediatric Research Conference, Columbus, Ohio, Ross Laboratories, 1956, pp. 87-91.

17. Hsia, D. Y.-Y.: The Laboratory Detection of Heterozygotes, Am. J. Human Genet. 9:98, 1957.

18. Hsia, D. Y.-Y.; Driscoll, K. W.; Troll, W., and Knox, W. E.: Detection by Phenylalanine Tolerance Tests of Heterozygous Carriers of Phenylketonuria, Nature, London, 178:1239, 1956.

19. Berenson, G. S., and Burch, G. E.: A Study of the Sodium, Potassium, and Chloride Contents of Thermal Sweat of Man Collected from Small Isolated Areas of Skin, J. Lab. & Clin. Med. 42:58, 1953.

20. Robinson, S., and Robinson, A. H.: Chemical Composition of Sweat, Physiol. Rev. 34:202, 1954.

21. Lichton, I. J.: Competition Between Sweat Glands and Kidneys for Salt and Water in Man, J. Appl. Physiol. 11:223, 1957.

22. Gochberg, S. G., and Cooke, R. E.: Physiology of the Sweat Gland in Cystic Fibrosis of the Pancreas, Pediatrics 18:701, 1956.

Testosterone-Induced Remission in Aplastic Anemia

NASROLLAH T. SHAHIDI, M.D., and LOUIS K. DIAMOND, M.D., Boston

Introduction

The treatment of aplastic anemia in childhood and adolescence has been one of the most hopeless and discouraging problems in the practice of pediatrics. In addition it has become a very worrisome problem since it seems to us that its incidence is increasing steadily. Review of the cases of aplastic anemia seen at the Children's Hospital during the past 20 years revealed that of 40 patients only 2 had a spontaneous remission and only one survived after four years. The others died from either generalized infection or hemorrhage. All therapeutic efforts have been uniformly unsuccessful. Transfusions, vitamin preparations, splenectomy, corticosteroids, and corticotropin have been tried singly or in combination, to no avail.

The aim of this paper is to describe a new approach to the therapy of this serious disease. For the past 16 months in addition to corticosteroid therapy and transfusion of platelets, fresh blood, and stored blood as needed, patients with proved aplastic anemia have been treated with testosterone. Rationale for this was based on the erythrogenic effect of testosterone observed in patients under treatment for breast cancer and myeloid metaplasia [1,2] and also in different animal species.[3] Another stimulus came from the occurrence of spontaneous remission in two boys beginning at puberty simultaneously with a spurt of growth and development and appearance of secondary sex characteristics.

Submitted for publication June 12, 1959.

Presented in condensed form at the meeting of the American Pediatric Society, Buck Hill Falls, Pa., May 8, 1959.

This investigation was supported in part by a grant (H 2405) from the National Institutes of Health and by the John A. Hartford Foundation.

Research Fellow in Medicine, Children's Medical Center, and Research Fellow in Pediatrics, Harvard Medical School (Dr. Shahidi). Associate Chief, Medical Service, Children's Hospital, and Associate Professor of Pediatrics, Harvard Medical School (Dr. Diamond).

Material and Methods

Five patients with severe aplastic anemia were treated with testosterone. The criteria for diagnosis were peripheral pancytopenia, aplasia of the bone marrow, and absence of lymphadenopathy or hepatosplenomegaly. The Table summarizes the pertinent hematologic features of each patient on admission.

The time elapsed between diagnosis and the start of testosterone therapy varied from six months to one year in four patients, during which they were treated with transfusions and corticosteroids without response. One patient was started on testosterone treatment a few days after the diagnosis was made.

Testosterone was used as testosterone propionate or methyltestosterone in the form of 10 mg. buccal Linguets in dosage of 1-2 mg/kg. body weight per

Hemogram on Admission

Case No.	Hemoglobin, Gm. %	Red Blood Cells, per Cu. Mm.	Hematocrit, %	Reticulocytes, %	White Blood Cells, per Cu. Mm.	Polymorphonuclears, %	Platelets, per Cu. Mm.
1	4.3	95,000	10.5	1	2,500	8	6,000
2	3.9	1,200,000		0.3	850	16	2,000
3*	8.8		24	2	2,250	21	30,000
4*	8.3	2,500,000	24	0.5	4,600	7	16,000
5*	9.6	3,000,000	28	0.7	3,200	8	5,000

* Received transfusion outside prior to admission.

day. In addition one patient was given testosterone enanthate intramuscularly at the dosage of 3 mg/kg. twice weekly. Corticosteroids were administered, in addition, as triamcinelone, dosage ranging from 12 to 8 mg. per day.

Blood counts were done by standard hematologic methods.

Erythrocyte survival studies were performed in two patients using sodium chromate containing radioactive chromium (Cr^{51}) by the method described by Necheles and associates.[4] The half-life of chromium activity on erythrocytes by this method ranges from 26 to 33 days in normal adults.

Report of Cases

Case 1.—A 7½-year-old white boy was admitted to the Children's Hospital on Aug. 27, 1957, because of lethargy and paleness of several weeks' duration. The past history disclosed that the patient had always been in good health until three months prior to admission, when he was noted to be pale and to bruise easily. No history of contact with any known toxic chemical agent or ingestion of known toxic antibacterial drug could be obtained.

Physical examination revealed an extremely pale, somewhat lethargic boy. The temperature was 99.8 F, pulse 120, and blood pressure 120/50. Skin was covered with petechiae and ecchymoses. There was no hepatosplenomegaly or lymphadenopathy. The hemogram on admission showed marked pancytopenia (Table). Bone marrow biopsy and aspiration revealed a markedly acellular specimen with depression of all elements and with some fatty replacement. On the basis of these findings the diagnosis of aplastic anemia was made. After a blood transfusion the patient was started on corticosteroids (prednisone, 40 mg. daily) and was discharged a week later to be followed in Out-Patient Clinic.

Continuation of corticosteroid therapy resulted in slight hypertension and marked weight gain, so the medication was discontinued temporarily. One month later the patient reentered in acute distress, covered with ecchymoses and bleeding from the mouth. He was given four units of fresh platelets, after which he improved and corticosteroid therapy was resumed. During the six-month period while on corticosteroids the patient required a blood transfusion almost every 15 days. The blood picture showed no significant change, and the bone marrow remained acellular and fatty (Fig. 1). Treatment with testosterone propionate buccal Linguets in a dosage of 40 mg. daily was begun on Feb. 10, 1958, and resulted in mild but sustained reticulocytosis, starting in about a month and reaching a peak of 14% after three months of therapy (Fig. 2). Bone marrow at this time revealed a hypercellular specimen with marked erythroid hyperplasia and with occasional young megakaryocytes (Fig. 3). The reticulocytosis was followed by a rise in hemoglobin, and no further transfusions were necessary. Continuation of therapy produced a steady rise of hemoglobin, which reached a peak of 14 gm. % after six months of therapy. In order to estimate the effect of testosterone and corticosteroids separately, all treatment was discontinued temporarily. Hemoglobin and reticulocyte levels then dropped abruptly. One month later the patient was placed on testosterone alone, which resulted again in reticulocytosis of 6%. However, since there was no noticeable rise in hemoglobin, it was felt that a hemolytic component might be present, and erythrocyte survival studies were performed. Chromium half-life of the erythrocytes at this time was found to be 17 days. The addition of corticosteroids resulted again in a rise of hemo-

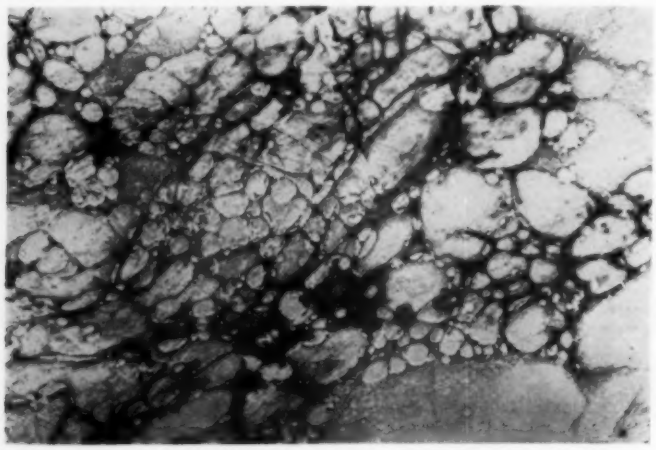


Fig. 1 (Case 1).—Photomicrograph (reduced about 32% from mag. × 90) of the bone marrow prior to the institution of testosterone therapy.

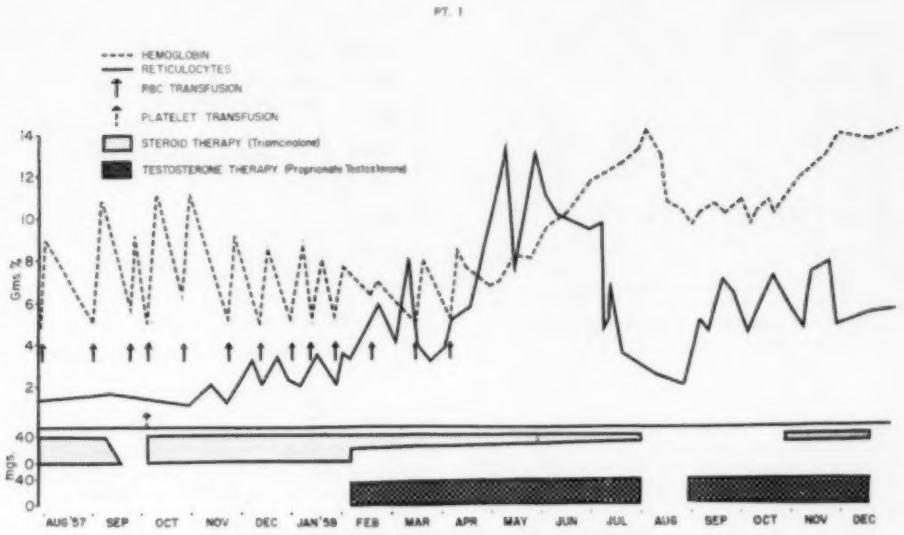


Fig. 2 (Case 1).—Reticulocyte and hemoglobin levels over a period of 17 months.

globin, and repeat survival studies now gave a chromium half-life of 21 days. With continuation of therapy, despite the high level of hemoglobin, the reticulocytosis persisted. On Jan. 1, 1959, all medication was discontinued again, and the hemoglobin dropped to 10 gm. % within a month. Then even without medication it rose gradually to 12 gm. %, and since has remained around this level. At present, the patient has not received transfusions for 14 months. His polymorphonuclears and platelets have improved markedly (Figs. 4 and 5) although they remain below normal range. The patient, however, does not show any sign of easy bruising or increased susceptibility to infection.

Case 2.—A 15-year-old white girl was admitted to the Children's Hospital Medical Service on Sept. 23, 1958, because of marked pallor, profuse vaginal bleeding, and generalized ecchymoses. The history disclosed that the patient had received large doses of chloramphenicol over a period of two months for a resistant staphylococcal infection.

Physical examination revealed a markedly pale and slightly lethargic girl. The temperature was 98.8 F, pulse 100, and blood pressure 110/75. The pertinent physical findings were numerous petechiae and ecchymoses on her skin and a Grade 2 soft systolic murmur heard over the precordium.

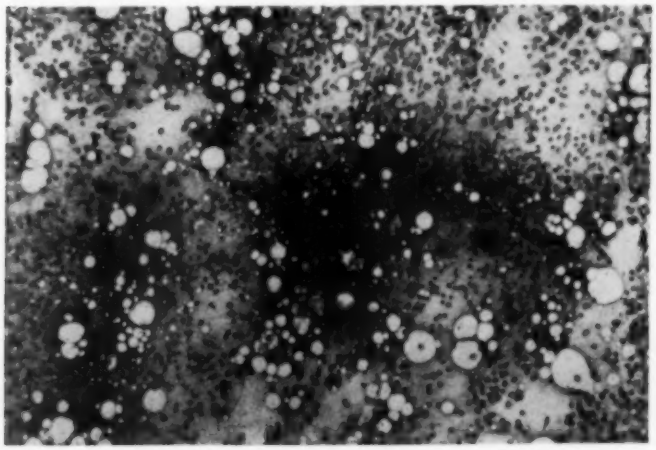


Fig. 3 (Case 1).—Photomicrographs (reduced about 32% from mag. × 368) of the bone marrow after three months of testosterone therapy.

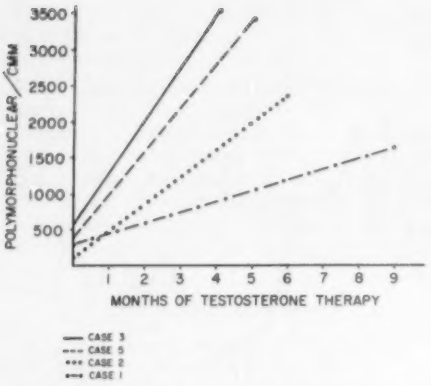


Fig. 4.—The absolute number of polymorphonuclears per cubic millimeter prior to testosterone therapy in each patient and the subsequent course while the patient was on this medication.

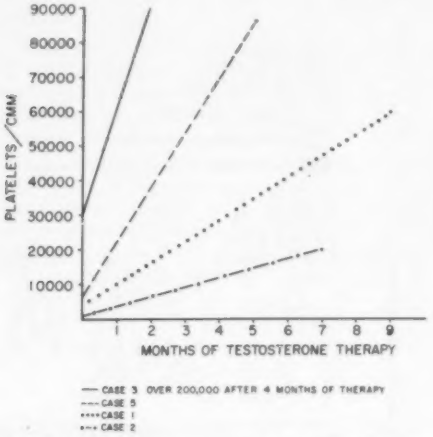


Fig. 5.—Platelet count prior to testosterone therapy in each patient and the subsequent course while the patient was on this medication.

The blood picture showed profound pancytopenia (Table). A bone marrow biopsy and aspiration revealed extreme hypoplasia of the marrow. On the basis of the history, blood picture, and bone marrow findings, a diagnosis of chloramphenicol-induced aplastic anemia was made.

On admission and the two days following, the patient received fresh whole blood transfusions, and was started on testosterone and corticosteroid therapy on Sept. 25, 1958. On this regimen the patient did quite well and her vaginal bleeding subsided. The continuation of medication resulted in a mild, very slow but sustained reticulocytosis, which reached a peak of 9% after six months of therapy (Fig. 6). Bone marrow aspiration at that time showed a hypercellular specimen with marked erythroid hyperplasia. During the first four months of therapy the patient required four transfusions, but finally in early February, 1959, without further transfusions the hemoglobin level stabilized at about 7 gm. % and then rose progressively to 10 gm. %. There has also been a steady increase in the number of polymorphonuclears (Fig. 4). The patient's platelets, however, remained low (Fig. 5). The patient is asymptomatic and shows no tendency to bleeding, and is still on the therapeutic regimen.

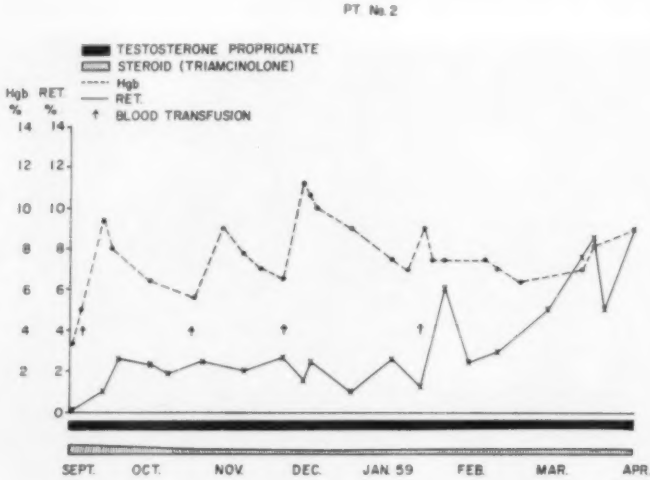


Fig. 6 (Case 2).—Reticulocyte and hemoglobin levels over a period of seven months.

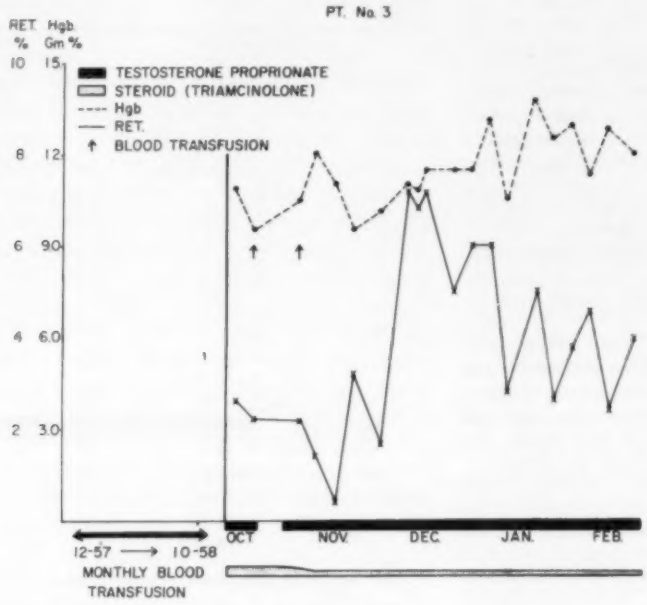


Fig. 7 (Case 3).—Hemoglobin and reticulocyte levels over a period of four months.

Case 3.*—A 5-year-old white girl had been in good health until December, 1957, when she was noted for the first time to bruise easily, and after this became pale. On the basis of the blood picture and bone marrow findings, a diagnosis of aplastic anemia had been made. From December, 1957 to October, 1958, in addition to an initial course of corticosteroids, the patient had received monthly blood transfusions. Seen for the first time at the Duke University Hospital in October, 1958, she was found to have anemia, thrombocytopenia, and leukopenia (Table). A repeat bone marrow study confirmed the diagnosis of aplastic anemia. In addition, the dark pigmentation of the skin, epicanthal fold, and bifid pelvis of the right kidney as revealed by intravenous pyelogram favored the diagnosis of Fanconi's aplastic anemia. Testosterone propionate in conjunction with corticosteroids was begun on Oct. 10, 1958.

During the next two months the patient's reticulocytes and hemoglobin rose progressively, and in January, 1959, she was found to have a hemoglobin level of 14 gm. % (Fig. 7). Here again, despite the high level of hemoglobin, the reticulocytes remained elevated. In addition there has been a remarkable improvement in the patient's polymorphonuclears and platelets (Figs. 5 and 6). A recent bone marrow aspiration corroborated the peripheral blood change in showing a markedly rich specimen with relative increase in erythroid elements.

Case 4.—The patient, a 5-year-old white boy, was referred on Oct. 10, 1958, to the Children's Hospital because of a diagnosis of aplastic anemia made in July, 1958, based on physical examination, blood picture, and bone marrow biopsy.

The patient had been well until early July, 1958, when he was noted to be pale and to bruise easily. On his admission to the local hospital, the hemogram disclosed pancytopenia. Bone marrow examination revealed a quite hypoplastic bone marrow. From early July, 1958, to early October, 1958, the patient had received cortisone, 300 mg. daily, and transfusions.

Physical examination disclosed a somewhat pale youngster with "moon facies." Temperature was 100 F, pulse 92, and blood pressure 130/72. There was no splenomegaly or lymphadenopathy. The liver edge was just palpable below the right costal margin. Skin was covered with numerous ecchymoses.

The hemogram on admission showed marked pancytopenia (Table). A bone marrow biopsy showed fatty replacement of bone marrow spaces with relative increase in lymphocytes. On the basis of these findings the patient was placed on testosterone propionate sublingually in addition to corticosteroids. During the four-month period on this regimen, despite some signs of masculinization, the patient did not show significant improvement.

* This case reported through the cooperation and courtesy of Dr. Doris A. Howell of Duke University.

He required multiple transfusions because of frequent nose bleeds. On February, 1959, he was started on testosterone enanthate intramuscularly, following which the hemoglobin remained fairly stable. Ten days later however, because of sudden and simultaneous occurrence of gastrointestinal bleeding and overwhelming infection, the patient died. Postmortem examination of the bone marrow revealed remarkable regeneration as shown by marked erythropoiesis. Erythropoietic activity was found also in the liver and in the spleen.

Case 5.†—A 7-year-old white girl was referred to the Children's Hospital on Nov. 13, 1958, because of a diagnosis of aplastic anemia made six months earlier.

History revealed that one and one-half years to six months prior to admission the patient had received chloramphenicol on six separate occasions. Six months prior to admission she developed ecchymoses followed by severe nose bleeds. Examination of the peripheral blood and bone marrow had revealed pancytopenia (Table). From May, 1958, to November, 1958, in addition to an initial course of corticotropin therapy of one month's duration, the patient was treated with corticosteroids and transfusions without noticeable change in her blood picture.

Physical examination revealed a somewhat obese girl with markedly rounded face. Temperature was 98.6 F, pulse 100, and blood pressure 120/80. The skin was covered with ecchymoses. There was no lymphadenopathy or enlargement of the spleen and liver.

The examination of peripheral blood showed no significant anemia since the patient had received a transfusion prior to admission, but severe thrombocytopenia and leukopenia with relative lymphocytosis were noted. Bone marrow examination revealed marked hypoplasia with hemosiderosis and plasmacytosis. There was a noticeable increase in fat particles. On the basis of the history and above findings diagnosis of aplastic anemia was confirmed, and in mid-November, 1958, the patient was started on testosterone propionate and triamcinelone.

Through the next two and one-half months she continued to have frequent nose bleeds requiring packing and blood transfusions. Finally in the beginning of January the nose bleeds subsided, and without further transfusion the hemoglobin rose progressively to 12.3 gm. % with a reticulocyte count of 6.6% at the end of March, 1958 (Fig. 8). The platelets rose from 5,000 to 85,000 and polymorphonuclears from 250 to 2,800 per cubic millimeter (Figs. 5 and 6). Concomitant with hematologic progress the patient has shown remarkable clinical improvement.

† We are indebted to Dr. James A. Wolff of the Babies Hospital, New York, for permission to present this case.

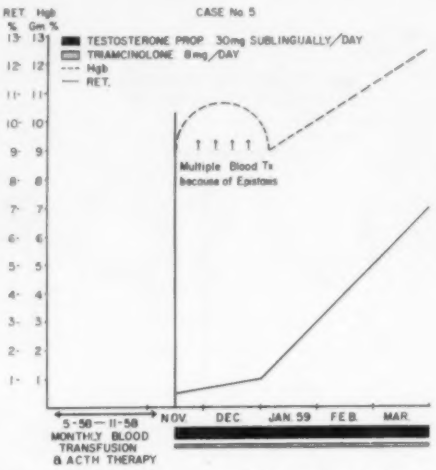


Fig. 8 (Case 5).—Hemoglobin and reticulocyte levels over a period of four and a half months.

Results

The reticulocytes and hemoglobin course of each patient is illustrated separately in Figures 2, 6, 7, and 8. It is apparent that reticulocytosis with subsequent rise in hemoglobin occurred in all except Case 4, who died. The postmortem examination of the bone marrow in this patient, however, showed signs of regeneration with erythroid hyperplasia. This was also found in the liver and the spleen. It is seen in the figures that the reticulocyte response did not occur shortly after the institution of therapy, as is often seen in other varieties of anemia given specific therapy. The time lapse between the start of treatment and the occurrence of a significant reticulocytosis ranged from one to two months, in Cases 1, 3, and 5, to five months in Case 2.

The reticulocytosis was accompanied or succeeded in all instances by a rise in hemoglobin, so that further transfusions were unnecessary. The lapse of time between the beginning of testosterone therapy and the last transfusion ranged from one to four months in all patients. In Cases 1 and 2 the rise of hemoglobin did not follow in the usual manner but only after a delay. The discrepancy between the reticulocytosis and hemoglobin rise became more con-

spicuous in the first patient in September, 1958, when he was given testosterone alone. Despite reticulocytosis of 6%, there was no noticeable rise in hemoglobin. Erythrocyte survival studies at this time showed a chromium half-life of 17 days. The erythrocyte survival studies performed on Case 2, who also showed similar delay in hemoglobin response, revealed a chromium half-life of 19 days. However, continuation of treatment with testosterone and corticosteroids produced steady increase in hemoglobin in all patients, reaching a peak of 14 gm. %, after six months of testosterone therapy in Case 1 and three months in Case 2. At the start of the hematologic response abnormal erythrocyte shapes and mild hypochromia, despite normal or high serum iron, was observed in most patients. These abnormalities, however, subsided subsequently.

Figure 5 indicates the platelet count prior to institution of testosterone therapy in each patient and the subsequent course during this medication. It is seen that rise of platelet levels varied greatly in these patients. In Case 3 with an initial platelet level of 30,000/cu. mm., there was remarkable improvement so that the platelet count reached over 200,000/cu. mm. after four months of therapy. In Case 2 the initial platelet level of below 2,000/cu. mm. showed only a slight but probably a significant response after five months of therapy.

Figure 4 summarizes the absolute number of polymorphonuclears per cubic millimeter in the same fashion. As is seen, all the patients showed significant improvement, and two of them reached normal levels.

Bone marrow aspiration and biopsy obtained in these patients prior to institution of testosterone therapy showed a markedly acellular and in most instances extremely fatty marrow, especially in patients who had been treated previously with corticosteroids. In a study of the course of the patient's bone marrow during testosterone therapy the following changes were observed: (*a*) appearance of mitotic figures in cells of erythroid origin within a month's period; (*b*) scattered foci of marrow regeneration with relative erythroid hyperplasia and reduction in fat particles within three months; (*c*) finally, at the peak of reticulocytosis, bone marrow aspiration showed a hypercellular specimen with marked erythroid hyperplasia and occasional young megakaryocytes. Figures 1 and 2 illustrates the bone marrow specimen from Case 1 obtained before and three months after testosterone therapy.

Side-Effects.—Acne, flushing of the skin, and mild hirsutism occurred in all patients two to three months after the institution of testosterone. The deepening and hoarseness of the voice, which occurred mainly in male patients, followed these dermal symptoms. None of the patients showed noticeable spurt of statural growth, but impressive gain in body musculature and strength was noted especially in boys.

On one occasion mild papilledema accompanied by headaches was noted in Case 2 without any other clinical manifestation. The only positive laboratory feature was an opening spinal fluid pressure of 500 mm. of H_2O obtained by lumbar puncture. These symptoms subsided with the use of a mercurial diuretic and chlorothiazide.

Changes in external genitalia and growth of pubic hair were more pronounced in boys and appeared from one to three months after therapy. In three patients whose bone ages were followed closely during testosterone therapy no discrepancy between the chronological age and the bone age was noted at any time. Figure 9 shows roentgenograms of the wrist of Case 1 at the age of 8 years, prior to therapy, and at the age of 9 years, after eight months of testosterone therapy. It is seen that the bone age corresponds closely to the patient's chronological age. Serum calcium and potassium levels in two patients showed no alteration, in contrast to reports by other investigators in patients receiving testosterone.[5,6] Serum PBI measured in two patients was also found to be within normal limits.

Fig. 9 (Case 1).—Roentgenogram of wrist (*a*) at the age of 8 years prior to testosterone therapy and (*b*) at the age of 9 years after eight months of testosterone therapy. Note that in both instances the bone age corroborates closely the patient's chronological age.

Concomitant with the progress of the bone marrow and blood picture these patients showed remarkable clinical improvement.

Comment

The observations made in these patients indicate that remission in aplastic anemia was induced by testosterone therapy. The bone marrow and peripheral blood studies revealed improvement to start with early erythroid regeneration and reticulocytosis. The rather slow reticulocyte response to therapy in these children can be explained in a variety of ways. First, it is obvious that aplastic anemia is different from the specific deficiency of iron-deficiency anemia or of pernicious anemia. Supplying the specific agent in these produces a prompt reticulocytosis. In aplastic anemia where bone marrow defect is mainly quantitative a quick response to therapy would seem unlikely. The repopulation of empty bone marrow spaces by cells undergoing mitotic division requires a certain period of time. In addition it should be borne in mind that testosterone, unlike vitamin B_{12} or iron, is not necessarily a specific agent for erythropoiesis, and as observed here the remission in these children was induced only after

Fig. 10 (Case 1).—*A*, patient on corticosteroids alone. *B*, patient on testosterone and corticosteroid. *C*, patient at the present time without any medication.

pharmacologic rather than physiologic doses. Furthermore, significant and time-consuming improvement in the bone marrow of these patients must develop before any noticeable changes appear in the peripheral blood.

It is of particular interest to note that in Cases 1 and 3, despite eventual high levels of hemoglobin, the reticulocytes remained elevated to about 6%. This finding suggests that testosterone could enhance the erythropoiesis even beyond physiological range.

The effect of sex hormones on erythropoiesis has been widely investigated. The results vary markedly with the species and amount injected. For instance, while large doses of estrogen produce a severe bone marrow aplasia in dogs,[7] monkeys seem to be refractory.[8] In normal animals the effect of the administration of hormones may be partially obscured by compensatory adjustments. In a spayed rat testosterone causes an increase in the number of erythrocytes, while estrogen produces marked anemia.[9] Injection of testosterone to hypophysectomized rats with anemia restores the red blood cells to normal, while estradiol aggravates anemia.[9] The injection of gonadotropic hormones results in a rise in the number of red blood cells in male and a fall in female rats.[9] A significant polycythemia with masculinization has been observed in mice afflicted with luteoma.[10] Thus in general it seems that, while estrogens produce anemia and aplasia of the marrow, androgens have strong erythropoietic action. In humans the erythrogenic action of testosterone has also been observed and stressed by several investigators. Kennedy and his associates [1,11] observed significant rise of hemoglobin in females with cancer of the breast treated with large doses of fluoxymestrone and methyltestosterone. The increase of hemoglobin did not seem always to correlate with improvement of cancer. Other investigators have observed similar results in patients with myeloid metaplasia having profound anemia who have been treated with testosterone.[2] Despite all this accumulated data, the exact mechanism whereby androgens stimulate erythropoiesis remains unknown.

Testosterone therapy also seems to have a beneficial effect on myelopoiesis as seen in our patients. It is obvious, however, that the rise of polymorphonuclears and platelets, although quite remarkable in certain instances, was not as dramatic as that of red cells (Figs. 4 and 5).

The corticosteroids so often used in patients with aplastic anemia have in our experience induced no beneficial effect when used alone. Similar results have been observed by Wolff,[12] who found that of 82 patients with aplastic anemia treated with cortisone, only 1 survived. However, when corticosteroids were given even in a small dose in conjunction with testosterone beneficial effects were definitely noted. The steroids certainly seem to improve thrombopenic bleeding. In addition, in one patient (Case 1), who showed a chromium half-life of 17 days while on testosterone alone, the addition of corticosteroids even in small doses, concomitant with a rise of red cell volume, resulted in a better erythrocyte survival (chromium half-life of 21 days). A hemolytic component in aplastic anemia is not an uncommon finding and has been noted by several investigators.[13,14] The increased rate of erythrocyte destruction in Cases 1 and 2 may explain the lack of an adequate rise of hemoglobin following reticulocytosis. Finally, the close correlation between the bone age and chronologic age in our patient, despite large doses of testosterone therapy during a long period of time, is of particular interest. It may be due to catabolic action of the steroids, which by opposing the anabolic effect of testosterone may prevent the increased maturation and premature closure of epiphyses.

The management of these patients should be regarded as an important contributing factor in success of testosterone therapy. For instance, large transfusions which increased the hemoglobin above 9 to 10 gm. % were found to depress the erythropoiesis markedly and were avoided. Fresh platelet and fresh whole blood transfusions were of

particular help and tided several of our patients over difficult periods of bleeding.

Summary

A new approach to therapy of aplastic anemia is described. Five patients with severe bone marrow failure were treated with combined testosterone and corticosteroids. Remission occurred in all except one, who died from simultaneous occurrence of gastrointestinal bleeding and overwhelming infection. The postmortem examination of the bone marrow, however, showed marked erythropoiesis even in this patient.

The bone marrow and peripheral blood studies in these patients revealed improvement beginning with early erythroid regeneration, then reticulocytosis with subsequent rise in hemoglobin. Beneficial effect of testosterone therapy was also noted on myelopoiesis. Concomitant with the progress of the bone marrow and the peripheral blood changes the patients showed remarkable clinical improvement.

300 Longwood Ave.

Addendum

Since the preparation of this manuscript, five other patients have been treated in the same manner. Two have shown a good response; one has shown moderate improvement, and two died two months after therapy was begun because of acute and generalized hemorrhage.

REFERENCES

1. Kennedy, B. J., and Nathanson, I. T.: Effects of Intensive Sex Steroid Hormone Therapy in Advanced Breast Cancer, J. A. M. A. 152:1135, 1953.

2. Pringle, T. C., Jr., and Gardner, F. H.: Treatment of Myeloid Metaplasia with Testosterone, Clin. Res. 7:210, 1959.

3. Gordon, A. S., and Charipper, H. A.: The Endocrine System and Hemopoiesis, Ann. New York Acad. Sc. 48:615, 1947.

4. Necheles, T. F.; Weinstein, I. M., and LeRoy, G. V.: Radioactive Sodium Chromate for the Study of Survival of Red Blood Cells, J. Lab. & Clin. Med. 42:358, 1953.

5. Kennedy, B. J.; Tibbetts, D. M.; Nathanson, I. T., and Aub, J. C.: Hypercalcemia, a Complication of Hormone Therapy of Advanced Breast Cancer, Cancer Res. 13:445, 1953.

6. Butler, A. M.; Talbot, N. B., and MacLachlan, E. A.: Effect of Testosterone Therapy on Concentration of Potassium in Serum, Proc. Soc. Exper. Biol. & Med. 51:378, 1942.

7. Tyslowitz, R., and Dingemanse, E.: Effect of Large Doses of Estrogens on the Blood Picture of Dogs, Endocrinology 29:817, 1941.

8. Tyslowitz, R., and Hartman, C. G.: Influence of Large Doses of Estrogens on the Blood Picture of Rhesus Monkeys (Macaca Mulatta), Endocrinology 29:349, 1941.

9. Vollmer, E. P., and Gordon, A. S.: Effect of Sex and Gonadotropic Hormones upon the Blood Picture of the Rat, Endocrinology 29:828, 1941.

10. Gottschalk, R. G., and Furth, J.: Polycythemia with Features of Cushing's Syndrome Produced by Luteomas, Acta haemat. 5:100, 1951.

11. Kennedy, M. D.: Fluoxymesterone in the Treatment of Advanced Breast Cancer, Cancer 10:813, 1957.

12. Wolff, J. A.: Anemias Caused by Infection and Toxins: Idiopathic Aplastic Anemia and Anemia Caused by Renal Disease, Pediat. Clin. North America, p. 469, May, 1957.

13. Bomford, R. R., and Rhoads, C. P.: Refractory Anemia, Quart. J. Med. 10:175, 1941.

14. Barker, W. H.: Excretion of Bile Pigment and Hepatic Function in Disease of the Blood, Arch. Int. Med. 62:222, 1938.

Emotional and Personality Development in Neuromuscular Disorders

MARVIN L. BLUMBERG, M.D., Rego Park, Long Island, N. Y.

The personality development of the child who is afflicted with a neuromuscular disorder from birth may differ greatly from that of normal children. The usual environmental and psychological factors that influence maturation are modified by the attitudes of other persons toward the disabled one and by his own attitudes toward his defects and the limitations which they impose upon him.

During the first few formative years, the normal child develops increasing physical independence as his motility and equilibrium patterns mature, enabling him to erect himself against gravity and to locomote independently. This growing capability is paralleled by the ego development and the appreciation of body image concept. The development of speech is a major step in communication and greatly facilitates the child's contact with his environment. The alteration of these patterns of maturation by central or peripheral neuromuscular disorders may influence profoundly the individual's personality. This results from the anxiety that is produced when organic illness disrupts the normal progress of such modalities as motor function, perception, and integration and, consequently, the ability to relate to reality.

Of all the neuromuscular disorders, cerebral palsy is most likely to be cataclysmic in its effects. It usually affects the child from birth with central brain damage. This central damage may affect only motor pathways or it may also compromise areas which will create perceptual difficulties or even impulsive behavior disturbances. At best, there is disruption of normal neural pathways which mediate coordination of effort and motility. Thus, the child will have to be taught and will have to accept conscious learning of patterns of motility and behavior which just evolve naturally in the normal child.

Bender [1] believes that motor development has extensive psychological implications in the dynamics of behavior and for the maturation of the child. His proper orientation in time and space, his appreciation of the world about him and his relationship to it are largely contingent upon the development of normal motor pathways and motility patterns. Posture, equilibrium, and maintaining a stance against the force of gravity are corollary functions to motility.

The tonic neck reflex is the first motor pattern to appear in the fetal infant. It is well developed at birth but inadequate for establishing posture and equilibrium, so the infant is dependent on the mother for these functions. Therefore, the grasping reflex is present primarily to maintain balance and to oppose the force of gravity but also to keep contact with the mother's body for warmth and nursing. There is a primitive relation between the grasping and sucking reflexes which mutually reinforce each other. These reflexes normally disappear with maturation but persist or return if certain areas of the brain are damaged, for example the prefrontal area.

Psychoanalytically, the grasping reflex apparatus is an important factor in the formation of the ego. The child becomes independent in equilibration and motility as

Submitted for publication Dec. 20, 1958.

From the Mental Hygiene Clinic, Queens General Hospital, Jamaica, N. Y., Frank Cerulli, M.D., Senior Psychiatrist.

a result of maturation of his brain and myelinated nerve tracts, and through the growth of his skeleton and musculature. Concomitantly, he normally renounces the libidinal gratification of contact with his mother. Bender [1] declares that unsolved motor problems related to security of equilibrium may produce anxiety neuroses later on.

Children with different types of central brain damage vary in their emotional reactions. Those with cerebellar lesions that cause asynergia and balance difficulties show an increase and prolongation of primitive postural and righting reactions which further interfere with their ability for independent locomotion. Bender has demonstrated that these children have a deep attachment to persons which is manifested by emotional and physical clinging. They feel markedly insecure when left alone. Extrapyramidal and basal ganglion (mainly striopallidal) pathology produce choreoathetosis and overresponsiveness to stimuli. Persons so afflicted must struggle to control their movements. Their attention is constantly focused on the problem of motility. They try to avoid stimuli and any enforcement of behavior patterns by others. Consequently, they tend to be resistive, negativistic, and unable to use personal relationships as the cerebellar cases do. The spastic children with pyramidal tract lesions have impaired use of their extremities but can adapt themselves to employ residual functions. They do not have difficulties with equilibrium and maintaining stance against gravity, so they are less clinging than cerebellar ataxics and less resistive than athetoids.

The child with muscular dystrophy presents a contrast in personality and disposition to the palsied child. Muscular dystrophy affects mainly the limbs. In the absence of asynergia of the trunk muscles and extraneous involuntary movements, there is less likelihood of loss of balance. There is no intensification of postural and righting reflexes with disturbances in posture. Therefore, the dystrophic child, although physically dependent, does not cling psychologically to those about him. Greene's [2] observations agree with Bender's in characterizing children with muscular dystrophy as generally well adjusted emotionally. Their behavior problems frequently stem from being overindulged and spoiled.

The brain-damaged child often experiences distortion of his body image concepts. Paul Schilder's definition of the human body image may be paraphrased as a gestalt picture of one's own body formed in one's own mind as a result of one's synthesis and interpretation of experiences and perceptions. Disturbances of body image may occur at different levels of development, perception, or integration. This can be influenced by organic disease, especially when it is accompanied by actual distortion of peripheral body structures, tonus changes and/or sensory changes. In cases of pathology occurring before or during birth or early in infancy, the child starts out with a potentially distorted body image. On the other hand, the older child who develops a neuromuscular condition consequent to encephalitis, poliomyelitis, and so on, may have another psychological problem in this respect. A discrepancy will exist between the established body image and the altered reality.

Lebovits and Lakin [3] found "body-image-related anxiety" to be characteristic of the paralytic poliomyelitis patients. They interpreted this as resulting from the conflict produced by the patient's attempt to retain his preillness body image as a reference point in the face of the realistic impairment which he was experiencing. These authors declare that even in the presence of major incapacity in paralytic poliomyelitis, afflicted persons do not suddenly or drastically alter their general body image concepts.

Language ability and facility are frequently affected in neuromuscular diseases which accompany cerebral pathology. The language function may be disturbed centrally by some form of sensory or motor aphasia. Moreover, the speech itself may

be dysarthric as a result of involvement of muscles of the mouth, tongue, larynx, chest, diaphragm, and so on, which mediate respiration, phonation, phrasing, and modulation of vocal sounds. These difficulties exist primarily in athetoid, less often in spastic cerebral palsy, occasionally following encephalitis, and in acute bulbar or respirator cases of poliomyelitis. Language and speech form the main method of communication and the chief means of making one's needs known. Therefore, any appreciable dysfunction of this modality creates frustration and discouragement.

It is interesting to compare and to contrast the emotional impact upon personality of an acute neuromuscular disease like poliomyelitis with that of infantile cerebral palsy. In poliomyelitis the disability strikes suddenly in a previously normal and unimpaired person. There is an acute phase of malaise, pain, and toxicity accompanying the paralysis and then a convalescent phase, with more or less improvement, merging into a rehabilitation stage with or without some degree of permanent impairment.

During the acute stage, the patient experiences reactions to the pain and disability as well as to the unexpected hospitalization. Robinson, Finesinger, and Bierman [4] describe the patient's adjustment to the hospital situation and treatment as associated in his mind with the somatic effects, the limitations of motility, and so forth. The emotional reaction may be influenced by an accompanying encephalitic process. Holland and Coles [5] write that lesions of the diencephalon, particularly in the hypothalamus, have been reported in as high as 85% of cases of bulbar poliomyelitis. Such lesions may cause emotional instability as well as autonomic disturbances of sleep, gastrointestinal functions, and so on.

Once the discomfort of pain has passed and the hospital is accepted, most children seem to be quite happy and rather oblivious to the significance of their paralyses. In the majority of adolescents and adults there is first a complete denial as the psychic mechanism of reaction to paralysis.[5] This is superseded by depression as convalescence and the institution of physical therapy bring realization of the actual disability. This experience is most uncommon in younger children.

Robinson et al.[4] have an interesting interpretation for the good behavior of the child poliomyelitis patient and his ready acceptance of hospital treatment and even immobilization. They claim that the child has guilt feelings as a reaction to the illness. He feels that this is a punishment for physical activity disapproved by his parents and that the punishment affects the very limbs that sinned. The child's compliance and submission to treatment seem to be atonement for the guilt.

Prugh and Taguiri [6] find evidence of heightened castration anxiety among adolescent poliomyelitis victims associated with alterations in body image. They also describe extreme denial and primitive fantasy as the usual early defense mechanisms in these patients.

All paralytic patients abandon hope of complete recovery most reluctantly, wishing to see themselves as before their illness. Robinson and Finesinger [7] discuss this as resistance to incorporation of change in self-perception. There is a time lag between the occurrence of the somatic changes and the patient's psychological acceptance of it. The mental reaction is relatively less severe in young children if they are emotionally stable. Paralysis, like any other traumatic experience, will affect a child psychologically in varying degrees, depending upon his previous and subsequent relationships and his security in the family environment. Pearson [8] considers the importance of parental attitudes and traumatic situations antedating or not directly related to the illness itself as factors affecting the child's own reaction to his disabilities.

Residual disabilities usually have their emotional impact as the child grows older. The severity of this emotional reaction may not necessarily be proportionate to the severity of the deformity and the disability but is dependent upon other personality

factors. Pearson further believes that serious illnesses have different psychic effects at various stages of development. During the latency period of about 7 to 10 years of age and during adolescence they are likely to produce first the reaction of denial, then overconcern and anxiety. During the prelatent period of early childhood, this author maintains, the effects of severe disabling illness are frequently severer, although less evident at the time.

So far, the intrinsic developmental substratum of the personality and emotional life of the neuromuscularly handicapped child have been stressed. Now, the extrinsic environmental factors must be considered, for in its total pattern personality is the result of interaction between the individual and his milieu.

From the moment that the infant is discovered to be abnormal, the attitude of the parents is affected. Sometimes there is rejection of the child. More often there is overprotection and dedication to the child to the extent of self-abnegation or psychological neglect of normal siblings. Frequently there are parental guilt feelings for moral, superstitious, or subconsciously motivated reasons. Every stage of rearing with its physical and psychological implications becomes a problem of great magnitude and perplexity.

The early handicapped child, such as one with cerebral palsy, has not only motility or speech difficulties. He will be limited in the social experiences which are familiar to the average child. He will have no personal acquaintance with running, physical play and contest, many toys, traveling away from home, and meeting many adults and children. This lack of social experiences has a definite stultifying effect on personality and even on intelligence test scores. Berko [9] indicates that most intelligence test materials utilize concepts based upon environmental experience. Other tests which attempt to minimize or to eliminate verbal and even motor performance tasks, depend upon perception, abstraction, and categorization, such as in the Columbia Mental Maturity Scale, which presents cards with geometric design figures. In the former tests, lack of social experience penalizes the subject. In the latter, visual perceptual deficits may do so. This is an objective counterpart of the child's subjective adjustment difficulties.

The prolonged dependence of the handicapped child, which is often accompanied by difficulties in communication, creates a unique relationship between the child and his family, and between him and the rest of society. Cruickshank and Bice [10] reviewed these interrelated factors as they influence personality development.

Parents ordinarily derive emotional gratification from contributing to their child's development and from their child's responses to them. If the child is handicapped, the parents' attention and emotional reactions are focused on the defect and the disability rather than on the child as a person. Anticipating the child's wants and giving to him tend to become emphasized as the way that the parents can express their love and gain satisfaction from the relationship. The consequent overprotection and overindulgence result in protracted dependency beyond the point of actual necessity. Further, there is continuous physical contact between the handicapped child and his parents for the purpose of moving about, dressing, feeding, toileting, and physical therapy. This profoundly affects the libidinal relationship of the child to the parent, usually the mother, and may retard his normal ego development. This has already been mentioned in connection with the grasp reflex and maintenance of equilibrium.

The young child does not realize the extent or significance of his handicap. Although the opportunity to compare himself with normal siblings and other children exists, he is slow to accept the concept of himself as deficient. As the child grows older, his awareness of his difference increases. He may find it increasingly difficult to relate to reality and to identify with normal coevals. The struggle to achieve normal maturation becomes intensified. The recognition of variance may lead to anxiety,

frustration, and withdrawal. The child may even develop a reaction of aggression against his environment or himself. It should also be noted that frustration tolerance is diminished in many brain-damaged persons on an organic basis, regardless of emotional factors.

The perceptual deficits which often accompany his other disabilities exert a very important influence on the social adjustment of the brain-damaged child. He has trouble in perceiving stimuli and integrating them into concepts of the world about him. Any or several sensory systems may be affected —visual, auditory, tactile, and kinesthetic. Silver [11] comments, "While the child with a predominantly motor disability is obviously crippled, the brain damaged child is more subtly crippled. He is, in effect, a perceptual cripple." The existence of perceptual and integrative defects often produce behavior disturbances and impulse disorders which augment the child's difficulty in adjusting to his society and which aggravate society's antipathy toward him.

The lack of appreciation of his physical disabilities and their attendant limitations rather than unawareness of them, allows the handicapped child to have aspirations for the future commensurate with his social exposures and experiences very much like those of the unhandicapped child. However, with the approach of adolescence and the growing consciousness of reality, there is often a more practical consideration of future plans based upon residual or rehabilitated abilities. This was illustrated by the results of the following inquiry.

Twenty-five children in a school unit for cerebral palsy and other severe neuromuscular handicaps were used as subjects. They came from different social, economic, and intellectual backgrounds. They varied in age from 5 to 14 years and in I. Q. from 69 to 135. There were 16 girls and 9 boys. Yet they had several features in common. They were all rather severely handicapped physically in one or more ways. They had all been having frequent, intimate contact with medical care and related modalities of

Factors Related to Future Ambitions of Children with Severe Physical Handicaps

Case No.	Age	Sex	IQ	Diagnosis	Ambition	Remarks
1	7	F	96	Athetosis	Nurse	
2	8	F	AH	Sp. quad.	Nurse	
3	8½	F	86	Sp. quad.	Nurse	
4	9	F	78	Sp. quad.	Nurse	
5	7	F	82	Sp. dipl. Meningomyelocele	Teacher	Repaired in infancy
6	8	F	69	Sp. quad.	Teacher	
7	6	M	79	Sp. quad.	Doctor	
8	8	M	117	Sp. quad.	Doctor	Father is physician
9	5	M	BA	Sp. dipl.	Daddy	
10	7	M	Av	Sp. quad.	Cowboy	
11	8	M	77	Sp. dipl.	Doughnut maker	
12	9	M	86	Sp. quad.	TV announcer	Unimpaired speech
13	5	F	120	Fl. dipl.	Does not know	
14	8	F	138	Sp. quad.	Does not know	
15	11½	F	104	Athetosis	Nurse	
16	12	F	79	Athetosis	Stay home, sew	
17	12½	F	80	Ataxia	Housewife	
18	14	F	77	Sp. quad.	Wanted nurse	Now realizes cannot
19	16	F	81	Sp. quad.	Telephone operator	Fairly good hands
20	10	M	104	Sp. dipl.	Wanted policeman	Changed mind, cannot
21	12½	M	135	Ten. ath.	Drummer in band	Encouraged by adult friend
22	16	M	87	Athetosis	Own business — pony ring	Like uncle's business
23	10	F	121	Sp. quad.	Does not know	
24	10	F	77	Arthrogryphosis	Does not know	
25	10	F	98	Ataxia	Does not know	Measles encephalitis

Key: AH=average to high average; BA=below average; Av=average; Sp. quad.=spastic quadriplegia; Sp. dipl.=spastic diplegia; Fl. dipl.=flaccid diplegia; Ten. ath.=tension athetosis.

therapy. All had experiences outside the home situation.

These children were each asked individually the simple question, "What do you want to be when you grow up?" Their answers are summarized in the Table.

Of the 14 children under 10 years, 4 girls (1 athetoid, 3 spastic quadriplegic) wanted to be nurses; 2 spastic girls (1 diplegic, 1 quadriplegic), teachers; and 2 spastic quadriplegic boys, doctors. One of the latter was the son of a physician. There were four spastic boys who respectively wished to be a "daddy" (diplegic), a cowboy (quadriplegic), a doughnut maker (diplegic), and a television announcer (quadriplegic). The last one did have good, unimpaired speech. There were two girls (one flaccid diplegic, one spastic quadriplegic) who could not be persuaded to express any future ambition at all.

The 11 children over 10 years indicated by their responses introspection as well as environmental influence. There was one exception, an 11½-year-old intelligent girl with severe athetosis who still wanted to become a nurse. One 12-year-old athetoid girl wanted to stay home and sew, and a 12½-year-old ataxic girl wanted to be a housewife. A 16-year-old spastic quadriplegic girl with fairly good hand function desired to become a telephone operator. A 14-year-old spastic quadriplegic declared that she had wanted to become a nurse but now realized that her condition would prevent this. Three 10-year-old girls adhered to their answers of, "I don't know." Their diagnoses were respectively, spastic quadriplegia, congenital arthrogryphosis and postencephalitic (measles) ataxia.

There were three boys in the older group. A 16-year-old severe athetoid wanted his own business, owning horses, probably a pony ring like his uncle's. A 12½-year-old severe athetoid had wanted to be a chemist but relinquished this idea in favor of becoming a drummer in a band as a result of an adult friend likening his movements to those of a jazz drummer and encouraging him in that direction. A 10-year-old spastic diplegic had wanted to be a policeman but changed his mind about that and had no new ambition yet.

While this survey is brief and the analysis of the data is mainly qualitative, they do bear out certain contentions that have already been made. Several interesting conclusions may be drawn from an examination of the answers. First of all, the responses to the question seemed to bear no correlation to the intelligence (i. e., I. Q.) of the children or to the type or severity of their disabilities. Secondly, the aspirations that they expressed were influenced by their life experiences as with normal children. Thirdly, the children under 10 years expressed the usual ambitions of childhood, especially unrealistic in view of their conditions, while those over 10 years mostly showed transitional or more practical thoughts about their future careers. Thus, within the intellectual and social range of this group, chronological age seemed to be the most important factor in creating awareness of the implications of the disabilities.

Adolescence is normally a time of ferment, when the individual is no longer a child nor yet an adult. Coincident with his growing cognizance of the role that he must play in society and of the social, economic, and other problems which begin to materialize, the adolescent tries to emerge from the dependencies and protections of his childhood. This is often accompanied by episodes of depression and emotional storms. The physically handicapped person has an even more difficult adjustment to make. When he should begin to develop independence and when family and society would want this, he is not yet physically or necessarily emotionally ready to do so. Social acceptance or even social tolerance may become quite strained. The frustration felt by the family is liable to increase as the physical and financial burdens grow with apparently diminishing returns.

Another point to consider is that the status of the severely handicapped adolescent does not change greatly, but that of

the mildly or moderately afflicted youth often becomes worse. The former will always be dependent without any expectations of competing for a livelihood. The latter, however, must now compete with the nonhandicapped in school, in business, and in industry.

The emotional development of the physically handicapped and the intrinsic and extrinsic factors which influence it should be taken into account in formulating any constructive programs. Even a handicapped child is an integral part of the society in which he lives. There is mutual impact and interaction. The more civilized and advanced a society is, the more tolerant it will be and, sometimes, the more provident it will be. This holds true at the administrative level and among enlightened groups. Yet, there is bound to be a great amount of rejection or apathy from casual observers. These attitudes affect the parents and their children in one way or another. Furthermore, many crippled children will be charges on society eventually. Some can be rehabilitated to become more or less self-supporting and contributing to the common weal. Others must always be cared for custodially. To these ends there have to be special schools that include various modalities of therapy—physical, occupational, and speech. For the older persons there must be vocational guidance, sheltered workshops, and special recreational facilities.

Coordinated effort is necessary on the part of medical and social agencies together with private practitioners in order to treat early and to rehabilitate the afflicted persons. The earlier the problems are recognized and evaluated and the earlier treatments and guidance are instituted, the better are the chances for achieving integrated personalities.

Summary and Conclusions

Neuromuscular disorders affect the emotional and personality development of the child. He reacts to his disabilities and to the limitations that they produce. He has to cope with the attitude of others toward him. Furthermore, he may show perceptual defects and occasionally organic behavior disturbances as a result of brain damage.

Disturbances of equilibrium and motility tend to prolong emotional dependency on parents or parent substitutes.

Spastic, athetoid, ataxic, and muscular dystrophic children present certain differences in emotional reactions to their diseases.

The child with extensive neuromuscular deformities usually has distortions of his body image concept.

Impairment of language ability and facility resulting from central and/or peripheral pathology often accompanies neuromuscular diseases. This prevents adequate communication with his environment and may aggravate the child's general frustration.

There are interesting comparisons and contrasts between the emotional repercussions in chronic neuromuscular disorders and those in acute paralytic poliomyelitis with its sequelae.

Intrinsic individual and extrinsic environmental factors interact in the development of personality. A three-way relationship exists among the afflicted person, his parents, and society.

The lack of social experiences and perceptual deficits have a stultifying effect on a child's intelligence and on his psychometric performance.

Brain damage may produce behavior disturbances which jeopardize the involved child's acceptance by society.

In childhood, there is a lack of appreciation of disabilities and their implications. The impact of reality begins to be manifested with the approach of adolescence. An interesting aspect of this fact was revealed in an inquiry among physically handicapped children concerning their future aspirations.

In order to achieve the optimum in emotional and personality development for the handicapped, it is important to recognize early the social and emotional factors as well as the physical aspects, and to elaborate

broad, coordinated programs for guidance and therapy.

98-120 Queens Blvd.

REFERENCES

1. Bender, L., editor: Psychopathology of Children with Organic Brain Disorders, Springfield, Ill., Charles C Thomas, Publisher, 1956.

2. Greene, J. L.: Emotional Factors in Children with Muscular Dystrophy, in Proceedings of First and Second Medical Conferences, Muscular Dystrophy Association of America, 1956.

3. Lebovits, B. Z., and Lakin, M.: Body Image and Poliomyelitis: An Experimental Approach, J. Nerv. & Ment. Dis. 125:518-523, 1957.

4. Robinson, H. A.; Finesinger, J. E., and Bierman, J. S.: Psychiatric Considerations in the Adjustment of Patients with Poliomyelitis, New England J. Med. 254:975-980, 1956.

5. Holland, J. C. B., and Coles, M. R.: Neuropsychiatric Aspects of Acute Poliomyelitis, Am. J. Psychiat. 114:54-63, 1957.

6. Prugh, D. G., and Taguiri, C. K.: Emotional Aspects of the Respirator Care of Patients with Poliomyelitis, Psychosom. Med. 16:104-128, 1954.

7. Robinson, H. A., and Finesinger, J. E.: A Framework for the Psychopathology of Poliomyelitis, Nerv. Child 11:10-17, 1956.

8. Pearson, G. H. J.: Emotional Disorders of Children, New York, W. W. Norton & Company, Inc., 1949.

9. Berko, M. J.: The Measurement of Intelligence in Children with Cerebral Palsy: The Columbia Mental Maturity Scale, J. Pediat. 47: 253-260, 1955.

10. Cruickshank, W. M., and Bice, H. V.: Personality Characteristics, in Cerebral Palsy, edited by W. M. Cruickshank and G. M. Raus, Syracuse, N. Y., Syracuse University Press, 1955, Chapt. IV, pp. 113-165.

11. Silver, A. A.: Diagnosis of the Various Syndromes Encountered in the Retarded Pre-Adolescent Child. Proceedings of the Thirty-Fifth Conference of the Child Research Clinic of the Woods Schools, Philadelphia, 1953.

Giardiasis, a Cause of Celiac Syndrome

JEAN A. CORTNER, M.D., Nashville, Tenn.

Introduction and Review of the Literature

For many years the pathogenicity of Giardia lamblia has been questioned. While these organisms are usually harmless saprophytic flagellates, it has been thought by many that in heavy infestation they cause an interesting spectrum of disease. The asymptomatic carrier appears at one extreme and the full-blown celiac syndrome at the other. In between are all degrees of abdominal pain, anorexia, nausea and vomiting, malaise, melena, gallbladder colic, jaundice, malnutrition, and diarrhea.

While the prevalence of Giardia lamblia infestation in children varies in different areas of the country, in most parts it exceeds 3%. In many areas of the southern United States [2-5] it rises as high as 20%. It is the low prevalence of symptoms attributed to Giardia infestation by clinicians which has caused many parasitologists to doubt its pathogenicity.

In support of the intermediate group in the spectrum of disease due to Giardia infection, Nutter,[6] Maris and Bushong,[7] Brown,[8] Fraser and Taylor,[9] Bøe,[5] and Hartman and Kyser [10] all report large series of children and adults found to have giardiasis during the investigation of gastrointestinal symptoms. Each reports more than 95% success in eradication of both symptoms and the Giardia after treatment with quinacrine (Atabrine).

McGowan,[11] Hartman and Kyser,[10] Drenckhahn,[12] Lyon and Swalm [13] report gallbladder colic and jaundice in patients with giardiasis, both of which subsided after treatment with quinacrine. Two theories of the pathogenesis of jaundice in such cases are (1) obstruction of the bile ducts caused by sheer numbers of parasites; or (2) irritation and edema of the ampulla of Vater resulting from attachment of the Giardia to the adjacent mucosa.

It is known that Giardia live optimally in an environment of pH 6.38-7.02, which the duodenum and upper jejunum supply.[14] Both clinical and pathological evidence demonstrates that the trophozoites attach themselves to the mucosal surfaces of the duodenum and upper jejunum by their peristomes. Their bodies and flagella are in constant motion since they feed primarily by absorption. It would seem logical, then, to suppose that mild infections produce upper gastrointestinal symptoms, if any, and that the severer infections cause upper gastrointestinal malabsorption.

Miller [15] in England was the first to report celiac-like disease due to giardiasis in 1926. He classified lambliasis into three categories: (1) asymptomatic, (2) mixed condition (i. e., associated with another disease), and (3) chronic Lamblia enteritis. It is interesting to note that two of his patients in the "mixed" category were considered to have true celiac disease. Of chronic Lamblia enteritis he concluded, "This can mimic celiac syndrome more than any other disease."

In 1938 and 1940 Véghelyi described the symptoms of giardiasis.[16,17] He reported one case in a 25-month-old boy who had had typical celiac syndrome from the age of 3 months, and, after being found to have giardiasis, made a complete recovery following treatment with quinacrine. Véghelyi documented this case with fat balance

Submitted for publication Jan. 21, 1959.

From the Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, and Babies Hospital, Columbia-Presbyterian Medical Center, New York.

studies, performed before, during, and after treatment with quinacrine. He further showed that children infected with Giardia with only minimal symptoms not suggestive of celiac disease may have markedly reduced fat absorption. He postulated that the Giardia caused malabsorption by mechanical obstruction of the mucosal surfaces of the duodenum and jejunum.

Roentgenographic findings similar to those seen in the alimentary tract in celiac disease or sprue have been reported by several authors.[18,19]

Sprue secondary to giardiasis has been reported in two adults.[20,21] At postmortem examination McGarth's patient[21] showed ulceration of the duodenum and jejunum and almost complete covering of their mucosal surface with Giardia attached by their peristomes. During life examination of several stools had failed to demonstrate Giardia cysts, although the duodenal aspirate contained thousands of Giardia trophozoites. Other authors emphasize the necessity of examining the duodenum aspirate to rule out this condition.

McGrath also reported a 9½-year-old boy with severe malabsorption who recovered after eradication of the Giardia lamblia.[22]

The last report in the American pediatric literature is that of Katsampes[23] in 1944 citing 12 cases from Rochester, N. Y. These patients did not show the full-blown celiac syndrome, but rather exhibited gastrointestinal symptoms, the investigation of which resulted in the finding of steatorrhea and giardiasis. All 12 cases had virtually flat vitamin A absorption curves which reverted to normal after treatment with quinacrine. The author controlled his results in cases of giardiasis by treating several true celiacs with quinacrine without beneficial clinical or laboratory effect.

The purpose of the remainder of this paper is to report four cases of giardiasis in which malabsorption of fat similar to that found in celiac disease was demonstrated; to confirm the observation that one cause

A 37-month-old girl (Case 1) with celiac syndrome caused by giardiasis.

of the celiac syndrome is infection with Giardia lamblia, and that subclinical infection may be dangerous to the host.

Report of Cases

Case 1.—A white girl was admitted to Vanderbilt Hospital on March 26, 1956, at the age of 3 years, 1 month. Her father was said to be in poor health in the Tennessee State Penitentiary; the mother and one younger sibling were living and well. The patient was the full-term product of the mother's first pregnancy, weighing 3,950 gm. at birth. There were no known prenatal or neonatal difficulties. Growth and development were normal until the age of 9 months, at which time she had a febrile illness diagnosed as meningitis, from which she recovered (the details of this illness are not known to us). Seen by a local physician at age 15 months, she gave a history of weakness, poor eating, failure to gain weight, failure to walk, and frequent large, foamy, foul, light-colored stools. Her weight at this time was 5,600 gm. Two stools were said to show no tryptic activity, and a barium enema revealed "large dilated loops of hypotonic bowel." She was treated with pancreatin (Panteric) granules and a high-protein, high-caloric diet with vitamin and iron supplements. She showed little improvement and at 3 years was referred to the Junior League Home in Nashville because of "failure to walk." Because of physical and mental retardation with steatorrhea she was referred to Vanderbilt Hospital.

Physical examination revealed a small, emaciated, unhappy, chronically ill child (Figure). Weight, 6.8 kg.; height, 72.4 cm.; head circumference, 44.5 cm.; chest circumference, 42 cm. The skin was pale and loose; inelastic folds were present over the abdomen, axillae, and extremities. The abdomen was moderately protuberant, soft, and elastic. The spleen tip was palpable 2 cm. below the left costal margin. Muscle power was poor, but the patient would walk with an unsteady gait when supported.

Laboratory Data.—Hemoglobin, 7.0 gm. per 100 ml.; hematocrit, 23.0%; RBC, 2,000,000 per cubic millimeter; MCV, 115 cubic microns, MCH, 35$\mu\mu$g., MCHC, 30%, WBC, 4,900 per cubic millimeter, with 49% segmented forms, 47% lymphocytes, and 0 eosinophils. ESR, 57 mm/hr. uncorrected (Wintrobe). Urinalysis was normal. Reticulocyte count, 4.8%. Serum CO_2, NPN, total serum protein with A/G ratio, calcium, phosphorus, and cholesterol were normal. A vitamin A tolerance test showed reduced absorption (fasting, Vitamin A=124 I. U/100 ml., carotene=15.2 mg/100 ml.; four hours, vitamin A=241 I. U/100 ml., carotene=0 mg/100 ml.; nine hours, vitamin A=126 I. U/100 ml., carotene=16.4 mg/100 ml.). Serum iron, 27μg/100 ml.; iron-binding capacity, 262μg/100 ml., and iron saturation, 9.3%. A bone marrow examination showed moderate megaloblastic arrest of the erythroid series with arrest of the granulocytic development at the early myelocytic stage. Three stools contained no ova or parasites, after which several stools were found to contain many Giardia lamblia cysts. The clay-colored, foul, bulky stools contained little fat and moderate starch by microscopic examination. Sweat chlorides were 26.5 mEq/L. by the method of Mauer and West. Duodenal aspirate liquefied gelatin in five tubes (interpreted as marasmic, not compatible with cystic fibrosis of the pancreas), and microscopic examination revealed numerous active forms of Giardia lamblia. Generalized demineralization of the long bones, shown in roentgenograms, was attributed to disuse atrophy. The first chest x-ray taken after admission showed no abnormality; subsequently the patient developed pneumonitis, which later cleared on tetracycline therapy.

She was treated with quinacrine 0.1 gm. daily for six days, folic acid 5.0 mg. p. o. daily, and a gluten-free diet. The Giardia cysts disappeared from the stools, and in the next 10 days she gained 1.25 kg. The reticulocyte count rose to 11.4% and then gradually fell to 2.2%. The blood indices returned to normal after one month of therapy. The serum iron rose to 126μg/100 ml., the iron binding capacity to 340μg., and the iron saturation to 24.9%. Treatment was continued in a convalescent home. The iron, folic acid, and gluten-free diet were discontinued after two months, at which time the patient's hemoglobin concentration had risen to 10.4 gm. per 100 ml. Four months after discharge from the hospital she weighed 11.25 kg. and was 79.4 cm. tall. The degree of retardation remains to be evaluated.

Case 2.—A white boy entered Vanderbilt Hospital on June 10, 1956, at the age of 19 months with the chief complaint of "failure to grow properly." Family history was noncontributory. Following a full-term, normal pregnancy and delivery he had respiratory difficulty, said to be due to "collapsing trachea," for which a tracheotomy was performed with relief of the respiratory distress. The tracheotomy tube had been left in place until admission to Vanderbilt Hospital. He was said to be well until 8 or 9 months of age, at which time he began to pass five or six large, loose, yellow, greasy, foul stools per day. His appetite remained good and he ate a balanced diet, but he failed to gain weight properly and gradually developed protuberant abdomen and muscle wasting. The only other symptoms were frequent colds and excessive sweating.

Physical examination revealed a poorly developed, poorly nourished child with a protuberant abdomen. Weight, 6,900 gm. The tracheotomy cannula was in place; there was no respiratory distress; the lungs were clear to percussion and auscultation. The liver edge was just palpable; the spleen was not enlarged. The remainder of the physical examination was within normal limits.

Laboratory Data.—Hemoglobin, 10.5 gm/100 ml.; ESR, 6 mm/hr. (Wintrobe method, uncorrected). FBS, serum NPN, CO_2 chloride, sodium, potassium, total serum protein and A/G ratio, calcium, phosphorus, alkaline phosphatase, protein-bound iodine were all normal. Three stools revealed Giardia lamblia cysts. Stool tryptic activity and duodenal tryptic activity were normal. Microscopic examination of the duodenal aspirate revealed numerous active forms of Giardia lamblia. Sweat chlorides, 27.0 mEq. per liter by the method of Mauer and West. A vitamin A tolerance test showed a flat curve (fasting, vitamin A, 132 I. U/100 ml.; 3 hour, vitamin A, 134 I. U/100 ml.; 5 hour, vitamin A, 114 I. U/100 ml.). Roentgenograms of the chest and the long bones were normal.

On removal of the tracheotomy tube the patient experienced no difficulty. He was treated with 50 mg. of quinacrine twice a day by mouth for five days and discharged on a regular diet. Subsequent examination of the stools failed to show Giardia cysts. In the course of eight months the patient gained 3 lb.; his stools became normal, and he showed general improvement in nutrition and development. The patient is believed to be of low normal intelligence.

Case 3.—This patient was first admitted to Babies Hospital in December, 1953, at the age of 10 months, with a history of vomiting and diarrhea for two months and swelling of the legs for two weeks. The family history was noncontributory. Except for retarded behavioral development the patient's past history was free from significant illness. The diarrhea was characterized by several loose, bulky, foul-smelling stools per day with no relation to meals.

On physical examination the patient was found to have a protuberant abdomen and a mild brawny edema of both pretibial areas. He weighed 7,270 gm.

Laboratory Data.—Blood cell count and urinalysis were normal. Serum electrolytes, NPN, and ESR were normal. A Mantoux test was negative. Plasma albumin, 3.6 gm. per 100 ml., globulin, 1.5 gm. per 100 ml. Stools contained ++ to +++ fat droplets, + fatty acid crystals, + to +++ extracellular starch, 0 to ++ intracellular starch, and a moderate number of red and white blood cells. Stool culture grew Salmonella tryphimurium.

He was treated with chloramphenicol (Chloromycetin) for five days, with the disappearance of pathogens from the stools, but his symptoms continued. Placed on a high-protein, low-fat, moderate starch diet he improved. Discharge weight, 7,870 gm.

Followed in celiac clinic from January, 1954, to May, 1955, he was never able to tolerate a regular diet without worsening of his stools.

On his readmission in May, 1955, when he was 2 9/12 years old, he was shown to have normal sodium and chloride concentration in his sweat, adequate trypsin in his duodenal aspirate, and a normal roentgenogram of the chest. Psychometric examination at age 34 months showed him to be functioning at a mental level of about 19 months. A gluten-free diet was tried on one occasion, with worsening of the stool pattern. In March, 1957, when he was 4 years old, many Giardia lamblia cysts were found in his stools. Therefore he was readmitted, and physical examination again revealed a celiac habitus. Weight, 17.3 kg. His fasting serum carotene level measured 36.0 mg/100 ml. His ability to absorb ingested fat was evaluated by an I^{131}-labeled fat absorption test[1] (Table). He was then treated with quinacrine 50 mg. three times a day for five days and discharged. Subsequent stools have revealed no Giardia lamblia on numerous occasions. At the time treatment with quinacrine was started he was put on a regular diet with no added vitamins, and since that time his stools have become completely normal; his weight gain has improved, and his abdomen is no longer protuberant. He was readmitted on April 29, 1957, one month after treatment with quinacrine, for repeat I^{131}-labeled fat absorption test (Table).

Admitted for the third time on Jan. 2, 1958, eight months after treatment, he showed a further improvement in fat absorption (Table). At this time the stool contained normal amounts of starch,

I^{131}-Labeled Fat Absorption Test Before and After Quinacrine Therapy in Cases 3 and 4*

	Per Cent Ingested I^{131} Fat in Serum					
	Case 3			Case 4		Normal †
Mo/Day Yr.	3/7 1957	5/1 1957	1/9 1958	4/30 1957	9/24 1957	
Hr. after ingestion						
2	0.8	1.7	1.8	1.6	3.7	3.8
4	1.7	2.4	3.3	3.6	3.6	5.5
6	1.6	1.8	3.2	2.1	2.1	5.8
24	1.8	0.6	1.6	1.0	1.0	1.8

* Test by the method of Malm, Reemtsma, and Barker.[1]

† As determined on normal children by Malm, Reemtsma, and Barker.

no fat droplets, no pathogenic bacteria, and no Giardia lamblia.

CASE 4.—A Negro boy was admitted to Babies Hospital for the first time April 12, 1957, at 22 months of age. The family history was noncontributory; the past history was within normal limits except for some delay in growth. His current problem related to repeated mild respiratory infections from the age of 2 months, with two bouts of bronchopneumonia requiring hospitalization and treatment with oxygen and antibiotics. Three days before admission he had developed another acute attack of bronchopneumonia.

His rectal temperature was 101 F; respirations 36 per minute; weight, 10,150 gm.; height, 80 cm. (each three standard deviations below the mean for his age and sex). He was acutely ill, had purulent rhinorrhea, enlarged tonsils and adenoids, cervical adenopathy, moderate respiratory distress, crackling inspiratory rales and occasional expiratory wheezes, and a moderately protuberant abdomen.

Hemoglobin, 9.2 gm/100 ml.; WBC, 9,200 per cubic millimeter, with 72% polymorphonuclears initially, and 6,700 to 8,450 with 20% to 30% polymorphonuclears, 40% to 42% lymphocytes, 7% to 14% monocytes, and 6% to 30% eosinophils after the acute infection subsided; MCV, 80 cubic microns; MCH, 21$\mu\mu$g., MCHC, 26.5%; urine, normal; zinc turbidity, 15.7 units/100 ml.; ESR, 16 mm/1 hr. (Westergren method); sickle cell preparation negative; serum albumin, 5.0 gm/100 ml.; serum globulin, 3.2 gm/100 ml. Mantoux test was negative. Nose and throat cultures grew no pathogens. Roentgenograms showed bronchopneumonia, which cleared, and pansinusitis, which persisted. Microscopic examination of the stool revealed +++ to ++++ intra- and extracellular starch, many Giardia cysts, no blood, and normal flora. Duodenal aspirate contained a few active forms of Giardia lamblia and 870 units of trypsin per milliliter; its pH was alkaline.

Two and one-half weeks after admission the patient was subjected to an I^{131}-labeled fat absorption test (for results see Table). After five days of treatment with quinacrine 50 mg. twice a day he was discharged.

With further observation in the clinic he was thought to be retarded in his convalescence by chronic tonsillitis. He was readmitted on Sept. 23, 1957 (five months after treatment with quinacrine), at which time he weighed 11.5 kg. No eosinophils were found in the peripheral blood and the stool contained no Giardia lamblia. An I^{131}-labeled fat absorption test was repeated on Sept. 24 (Table 1) and a T and A performed on Sept. 26.

Comment

Our four cases represent Giardia lamblia infection with clinically manifest malabsorption. The response after quinacrine therapy was unmistakable. Laboratory documentation of the improvement in absorption was attempted in two cases. In one the improvement was clear-cut and progressive, both at one and at eight months after therapy. The other showed improvement at the two-hour level five months after therapy, but further follow-up was impossible. It is unfortunate that urine collections were not made during the I^{131}-labeled fat absorption tests, for they have subsequently proved to be a more satisfactory estimate of fat absorption than serum levels.

There seems to be no doubt that giardiasis can be severe enough to interfere with absorption from the duodenum and upper jejunum and that rarely this can react to such a degree as to produce a picture resembling celiac disease.

Summary

Four cases of giardiasis associated with celiac-like malabsorptive disease (celiac syndrome) in children have been reported in detail.

The literature has been reviewed which suggests that giardiasis causes a spectrum of disease states extending from the asymptomatic infection to the full-blown celiac syndrome. In between are all degrees of upper gastrointestinal signs and symptoms; rarely gallbladder and hepatic signs and symptoms occur. This intermediate group of patients may experience reduced fat absorption without clinically evident malnutrition.

Quinacrine (Atabrine) in our experience, eliminates the infection and relieves all resulting symptoms.

Acknowledgment is made of the help of Drs. Harris D. Riley and Calvin Woodruff in giving encouragement to study the two patients from Vanderbilt, and to Drs. Rustin McIntosh and Amos Christie for reviewing the manuscript.

Vanderbilt University School of Medicine.

REFERENCES

1. Malm, J. R., Reemtsma, K., and Barker, H. G.: Comparative Fat and Fatty Acid Intestinal Absorption Test Utilizing Radioiodine Labeling: Results in Normal Subjects, Proc. Soc. Exper. Biol. & Med. 92:471, 1956.

2. Faust, E. C., and Headlee, W. H.: Intestinal Parasite Infections of the Ambulatory White Clinic Population of New Orleans, Am. J. Trop. Med. 16:25, 1936.

3. Belding, D. L.: Textbook of Clinical Parasitology, Ed. 2, New York, Appleton-Century-Croft, Inc., 1942, p. 144.

4. Meleney, H. E.; Bishop, E. L., and Leathers, W. S.: Investigations of Endamoeba Histolytica and Other Intestinal Protozoa in Tennessee, Am. J. Hyg. 16:523, 1932.

5. Bøe, J.: Occurrence of Human Intestinal Protozoa in Norway with Special Reference to Entamoeba Histolytica and Lamblia Intestinalis and Their Clinical Significance, Acta med. scandinav. 113:321, 1943.

6. Nutter, P. B.; Rodaniche, E. C., and Palmer, W. L.: Giardia Lamblia Infection in Man, J. A. M. A. 116:1631, 1941.

7. Maris, E. P., and Bushong, S.: The Diagnosis of Giardia Intestinalis Infestation by Means of Intestinal Intubation, Pennsylvania M. J. 45:724, 1942.

8. Brown, E. H.: Giardia Lamblia: The Incidence and Results of Infestation of Children in Residential Nurseries, Arch. Dis. Childhood 23: 119, 1948.

9. Fraser, J. F., and Taylor, R.: Diarrhea Due to Giardia Lamblia, Brit. M. J. 2:184, 1945.

10. Hartman, H. R., and Kyser, F. A.: Giardiasis and Its Treatment, J. A. M. A. 116:2835, 1941.

11. McGowan, J. M.; Nussbaum, C. C., and Burroughs, E. W.: Cholecystitis Due to Giardia Lamblia in a Left-Sided Gallbladder, Ann. Surg. 128:1032, 1948.

12. Drenckhahn, C. H.: Jaundice Associated with Giardia Lamblia Infestation, Illinois M. J. 83:119, 1943.

13. Lyon, B. B. V., and Swalm, W. A.: Giardiasis: Its Frequency, Recognition, Treatment and Certain Clinical Factors, Am. J. M. Sc. 170:348, 1925.

14. Haiba, M. H.: The pH of the Alimentary Tract in Normal and Giardia-Infected Culture Mice, Parasitology 44:387, 1954.

15. Miller, R.: Lambliasis as a Cause of Chronic Enteritis in Children, Arch. Dis. Childhood 1:93, 1926.

16. Véghelyi, P.: Giardiasis in Children, Am. J. Dis. Child. 56:1231, 1938.

17. Véghelyi, P. V.: Giardiasis, Am. J. Dis. Child. 59:793, 1940.

18. Peterson, G. M.: Intestinal Changes in Giardia Lamblia Infestation, Am. J. Roentgenol. 77: 670, 1957.

19. Welch, P. B.: Giardiasis with Unusual Findings, Gastroenterology 3:98, 1944.

20. Chaudhuri, R. N.: A Note on Giardiasis with Steatorrhea, Indian M. Gaz. 78:284, 1943.

21. McGrath, J.; O'Farrell, P. T., and Boland, S. J.: Giardial Steatorrhea: A Fatal Case with Organic Lesions, Irish J. M. Sc. 68:802, 1940.

22. O'Donovan, D. K.; McGrath, J., and Boland, S. J.: Giardial Infestation with Steatorrhea, Lancet 2:4, 1942.

23. Katsampes, C. P.; McCoord, A. B., and Phillips, W. A.: Vitamin A Absorption Test in Cases of Giardiasis, Am. J. Dis. Child. 67:189, 1944.

Chylous Ascites and Lymphedema

WARREN J. WARWICK, M.D.; RALPH T. HOLMAN, Ph.D.; PAUL G. QUIE, M.D., and ROBERT A. GOOD, Ph.D., M.D., Minneapolis

Acute chylous ascites with elephantiasis (lymphedema) is rare. This is the fifth case of this congenital syndrome to be recorded. There have been no reported cases of concurrent lymphedema and chylous ascites developing in older patients.

Report of Case

The patient was born to normal, healthy parents on March 28, 1952, after an uneventful pregnancy and spontaneous delivery. Birth weight was 8 lb. 4 oz. At the time of delivery, she had swelling of her entire left leg and right arm and a hemangioma lateral to her right eye. She was jaundiced for four days after birth. There was no family history of ascites, lymphedema, or hemangiomas. Two children born later have been completely normal.

Abdominal distention developed slowly and was not marked at her first hospitalization, when she was 5 months old. At that time, however, she had edema of the face, the right arm and hand, the left abdominal wall, and the left leg and foot. Roentgenograms of the right arm and left leg were consistent with lymphedema. Urine analysis, Klein, and Mantoux tests were negative. The hemogram was normal. Her total plasma protein was 5.1 gm., with 3.8 gm. of albumin and 1.3 gm. of globulin.

Between the ages of 5 and 45 months, she had nine hospital admissions for respiratory infections varying from a "slight cold" to severe pneumonia. Her other hospitalizations during these months are noted below.

Submitted for publication Feb. 10, 1959.

Aided by grants from the U. S. Public Health Service, the Minnesota Division of the American Cancer Society, and the American Heart Association.

From the Pediatric Research Laboratories of the Variety Club Heart Hospital, the Department of Pediatrics, and the Hormel Institute of the University of Minnesota. Professor of Physiological Chemistry, Hormel Institute, Austin, Minn. (Dr. Holman) and American Legion Memorial Heart Research Professor of Pediatrics (Dr. Good).

When 10 months old, she was admitted for study and treatment of her ascites and elephantiasis. Two paracenteses removed 2,000 and 600 ml. of milky fluid. Mantoux and routine urinalysis were negative. Blood tests revealed 13.2 gm. hemoglobin; 5,800 white blood cells, with 70% neutrophils, 22% lymphocytes, 4% monocytes, 3% eosinophils, and 1% basophils; 93 mg. % fasting blood sugar; 12.6 mg. % blood urea nitrogen; 238 mg. % serum cholesterol; 6.0 gm. serum protein, with 4.6 gm. albumin and 1.4 gm. globulin. The serum CO_2 and Cl were 22.5 and 101 mEq. per liter, respectively. The bleeding and clotting times were normal. An exploratory laparotomy was done. Large amounts of milky fluid were found filling the peritoneal cavity. The radix mesentericus contained firm, irregular masses which were covered with small, white, tortuous lines, thought to represent lymphatics filled with some fatty material. The masses had the appearance of fat necrosis and inflammation. The liver was normal. A biopsied specimen of one of the masses was composed of fat overlaid with yellowish white nodules of firm consistency. The microscopic sections showed fat supported by connective tissue stroma. Areas of the fat were replaced by irregularly shaped, large cells with foamy cytoplasm and small dense nuclei. A diagnosis of macrophage reaction in the mesenteric fat was made. There was no relief of the ascites after this surgical procedure.

During the next 10 months, progressively larger quantities of chylous ascitic fluid were removed by paracentesis at shorter intervals. A maximum was reached in December, 1954, when more than 18 liters were removed. On Figure 1 is shown the number of paracenteses done and the quantity of chylous ascitic fluid removed each month. During the next six months, the patient became weaker with a greater susceptibility to infection and a diminished appetite. On March 2, 1954, an upper gastrointestinal series showed subserosal thickening of the small bowel. Serum protein was 5.6 gm., with 3.7 gm. of albumin and 1.9 gm. of globulin. By May, 1954, the serum proteins had dropped to 4.3 gm., with 2.6 gm. of albumin and 1.7 gm. of globulin. By that date, she had had 50 paracenteses with the loss of 135 liters of chylous ascitic fluid. As a result of her reduced appetite and the cumulative loss of protein by paracentesis,

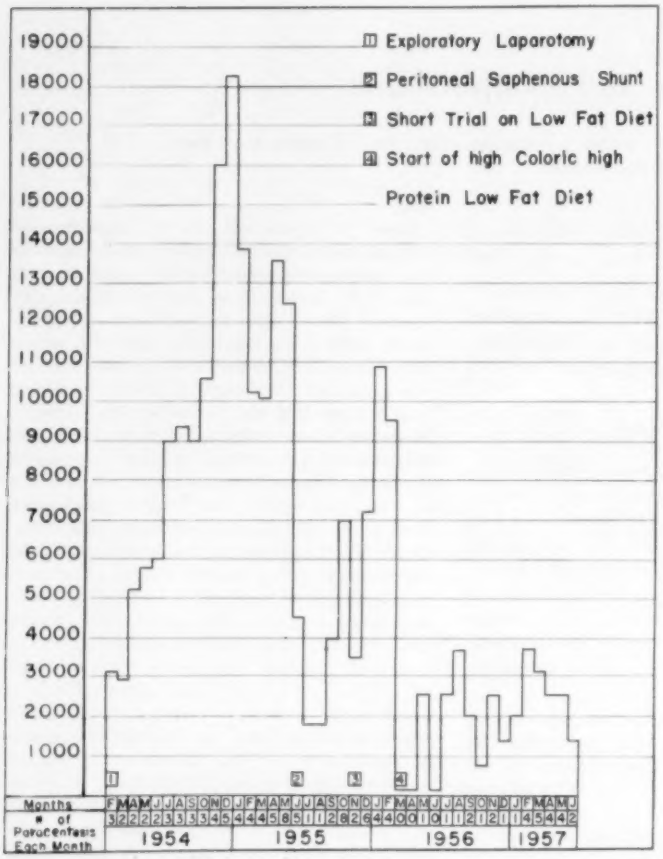


Fig. 1. — This graph plots the amount of fluid removed by paracentesis and lists the number of paracenteses required per month. It will be noted that peritoneal saphenous vein shunt temporarily reduced the loss from paracentesis and that high-calorie, high-protein, low-fat diet substantially reduced the loss of chylous ascitic fluid over a prolonged period.

she became so malnourished and weak that she could not walk. In hope of finding a lesion amenable to correction, she was readmitted to the hospital and prepared for surgery. Over a 10-day period, she was given seven transfusions of her own chylous ascitic fluid totaling 2,600 ml. These infusions produced a rise of 0.5 gm. in her serum albumin and an improvement in her clinical condition. After this, she was given three units of plasma and one of the salt-poor serum albumin, causing a further increase of 0.6 gm. of serum albumin.

On June 15, 1954, her chest and abdomen were explored. The right thoracic duct appeared small but normal. It was injected with iodopyracet (Diodrast) compound, which was shown by roentgenograms to be extravasated in the retroperitoneal tissues around the thoracic duct just anterior to the spine at the level of the diaphragmatic crura. The abdomen was explored carefully, especially the region behind the pancreas, but no cisterna chyli, dilated lymph vessels, or cause of lymphatic obstruction were found. The entire peritoneal surface was thickened, and there were some adhesions within the abdomen. The mesentery of the small bowel was thick, but there were no lymphatics within it, nor were there any lymph nodes in the small bowel mesentery. Beneath the serosa of the small bowel were tiny lacteals only a fraction of a millimeter in diameter, from which chyle could be expressed by pressure. The surface of the bowel appeared normal. Because no cause for the chylous ascites was found, a left saphenous vein-peritoneal anastomosis was performed.

Transient improvement resulted, but about a week after surgery it was noted that the ascites was returning. Another week later, it was necessary to relieve her distention by paracentesis. The partial success of the anastomosis was apparent during the following two months, when she required paracentesis only twice. But gradually the

ascitic fluid accumulated more rapidly and had to be removed more frequently.

During November, 1955, after an attack of pneumonia, she was placed on a low-fat diet. This resulted in what appeared to be a significant decrease in the quantity of chylous ascitic fluid produced. Serum protein at this time was 5.0 gm., with 3.4 gm. of albumin and 1.6 gm. of globulin.

First University Admission.—On Dec. 6, 1955, she was admitted to the Metabolic Research Ward of the University of Minnesota Hospitals. One of the purposes of this primary investigation was to evaluate the ascites-producing effect of her normal diet, as compared with a fat-free and a high fat diet. The rate of chyle formation was determined by paracentesis at varying intervals of time, each time attempting to remove all fluid. This was done seven times, both before and after the periods of testing, at intervals of from three to nine days. The average rate of production was 339±33 ml. per day, with a range of from 278 to 386 ml. per day. During the three-day period on a fat-free diet, 700 ml. of chyle accumulated intraperitoneally—an average of 233 ml. of chyle per day. When the same diet was continued with the addition of 30 gm. of Lipomul-Oral (a dietary supplement), 1,200 ml. of chyle accumulated—an average of 400 ml. of chyle per day.

The average daily accumulation of chyle on the low-fat diet was significantly reduced to 3.18 standard deviations below the average accumulation. However, with the added fat, even though the amount produced was almost double that produced on the low-fat diet and in excess of the above-noted range for daily chyle formation, it was only 1.83 standard deviations from the mean and not significantly increased. The chyle produced on the low-fat diet contained 1,470 mg. % of fat, compared to 1,350 mg. % on the high-fat diet.

It had been previously noted and it was confirmed during this admission that the patient's white cell differential normally contained 80% to 85% neutrophils and 10% to 15% lymphocytes. This persistently low proportion of lymphocytes and the known lymphatic anomalies prompted us to investigate aspects of her immune mechanisms.

Lymph node biopsies were obtained before and four days after two injections of 0.5 ml. of DPT and 0.5 ml. of T. A. B. immunizing vaccine, which were given at an interval of seven days. Concentration of antibodies against these antigens was determined prior to beginning injections and 11 days after the last injection of antigen. The increases in antibody levels are shown in Table 1. These increases are of the same magnitude as those obtained in normal children given the same series of injections. The patient was of blood Group O. Her naturally occurring anti-A isoagglutinins were positive in a dilution of 1:1,280. The lymph node specimens showed a normal reticular structure and a typical stroma. There was a normal response to the antigenic stimulation with proliferation of the germinal centers and an abundant increase in the number of plasma cells and the formation of secondary nodules. The Schick test was positive prior to the antigenic stimulation but changed to negative two weeks after the second of two injections of DPT vaccine. In addition, she had a normal cutaneous inflammatory response to scarification and a normal phagocytic activity of her leukocytes for pneumococcal organisms.

TABLE 1.—*Immune Response in Patient with Chylous Ascites and Lymphedema*

	Typhoid O	Typhoid H	Paratyphoid	Schick
Prior to Antigenic Stimulation	>1:40	>1:40	>1:40	++++
After Antigenic Stimulation *	1:320	1:640	1:320	Neg. †

* Injected on two occasions, one week apart, with 0.5 cc. T.A.B. and DPT, bled 11 days after last injection.
† Two weeks after the second injection of antigen.

The serum protein was 3.6 gm., with 1.6 gm. of albumin and 2.0 gm. of globulin. There was a total cholesterol of 108 mg. %, with the cholesterol esters representing 73 mg. %, or 68%. The total lipids were 19 units, CO_2 was 23, chlorides 107, sodium 135, and potassium 5.0 mEq. per liter. The calcium was 6.3 mg. %.

Simultaneous glucose tolerance tests on the blood and chyle showed the following:

Hours	Blood	Chyle
Fasting	81	88
½	105	88
1	132	87
2	109	91
3	90	97
4	81	93

An eosinophil response test showed a fasting level of 72 eosinophils per cubic millimeter and a four-hour level of 19 per cubic millimeter. In a vitamin A absorption test done with fatty vitamin A, the fasting level was 28 mg. % and the five-hour level, 38 mg. %. The blood carotene level was 34 mg. %. When this test was repeated with use of an aqueous vitamin A preparation, the fasting level was 14 and the five-hour level was 44 mg. %. No carotene was demonstrated in the blood.

Duodenal enzymes were aspirated. Trypsin activity was present in Tubes 4 to 9, lipase was equivalent to 17.15 cc. of 0.05 N NaOH, and

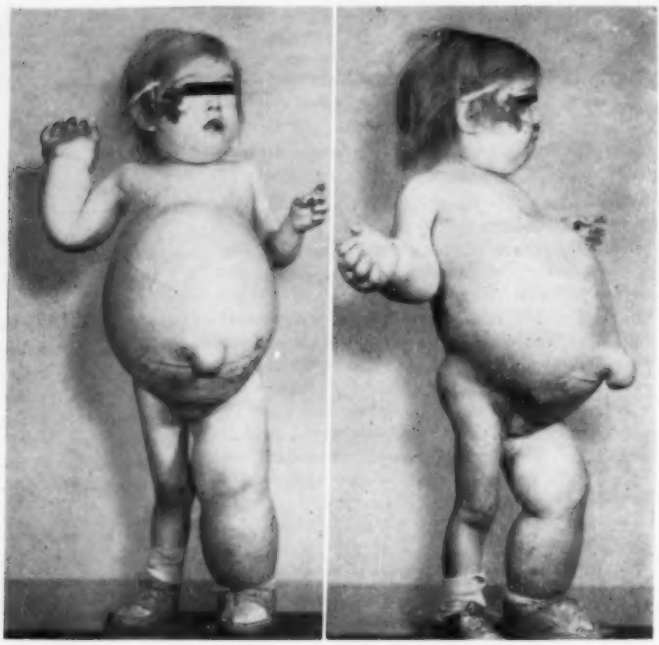


Fig. 2.—The patient at 3 years 11 months of age. Note the markedly distended abdomen, reflecting the chylous ascites, as well as the striking lymphedema of the right arm and left leg.

amylase was present 15 units per milliliter. The pH was 6.

The general appearance of the child is illustrated in Figures 2 and 3. The asymmetrical lymphedema and marked ascites are apparent.

Fig. 3.—Closer comparison of the striking lymphedema of the left leg and the normal right leg. The striking elephantiasis is apparent as is the site of a recent infection in the diseased leg.

Second University Admission.—During the two months after her discharge, the patient required eight paracenteses with the loss of close to 20 liters of chylous ascitic fluid. She became lethargic, weak, and inactive. Except for the day after the paracentesis, she was not able to walk or stand. It was apparent that her dietary intake was inadequate to maintain her nutrition in the face of such massive and continued loss of calories and protein. She was hospitalized again, this time for evaluation of the long-term effect of a high-protein, high-calorie, and low-fat diet.

It was desired to provide her with 1,500 calories, containing less than 10 gm. of fat a day. In Figure 4 is demonstrated the acceptability of the diet and its effect on the accumulation of chyle, as reflected by measurement of the daily weight. Her weight gain was about 150 gm. per day for the first 10 days, an even more striking reduction in the rate of chyle formation than had obtained on the trial fat-free diet. During this time, she was observed to become stronger and more active. In addition, she changed from a withdrawn and uncooperative child to one with a happy, pleasant disposition. A major reason for this, it seemed, was the gentle and friendly nursing care offered in the metabolic ward. Then her weight remained stable for eight days, after which, between the 20th and 30th days, she lost on the average 150 gm. per day, so that 30 days after starting the diet she weighed less than when it was begun.

TABLE 2.—*Paper Electrophoretic Values of Serum Proteins* *

	Before Special Diet		On Special Diet				
	12/8/55	1/11/56	4/4/56 33 Days	4/23/56 55 Days	5/5/56 67 Days	10/24/56 249 Days	Normal Values
Albumin	1.5	1.3	1.6	1.9	2.0	2.0	3.4-4.4
α-1-Globulin	0.2	0.3	0.4	0.3	0.3	0.2	0.1-0.3
α-2-Globulin	0.85	0.8	1.5	1.0	1.3	1.2	0.5-0.7
β-Globulin	1.1	1.1	1.7	1.4	1.3	1.4	0.7-1.1
γ-Globulin	0.6	0.4	0.8	0.9	0.85	0.9	0.8-1.4
Total Protein	4.25	3.9	6.1	5.6	5.75	5.7	5.5-7.9

* Expressed as grams per 100 ml. of serum.

With this, there was a marked softening of the edema in her right arm and left leg and a reduction in her abdominal circumference. But from the next day her weight and the several circumferences of her arms, legs, and abdomen increased constantly until her death.

Her total serum protein quickly returned toward normal, but there were rather persistent increases, both absolute and relative, of α-1-, α-2-, and β-globulins before the albumin and γ-globulin fractions rose.

During the 59 days in the hospital, her parents were instructed in low-fat cookery. Thereafter at home they were able to keep her intake at 1,200 to 1,400 calories with between 3% and 5% of these as fat.

Third, Fourth, and Fifth Hospitalizations.—On three occasions, 83, 146, and 167 days after starting the low-fat diet, she became ill with pneumonia. In each instance, recovery occurred after abdominal paracentesis and treatment with penicillin and tetracycline.

Sixth University Hospitalization (Sept. 30, 1956).

In addition to this apparently increased susceptibility to infections, ectodermal changes appeared which were suggestive of a deficiency of unsatu-

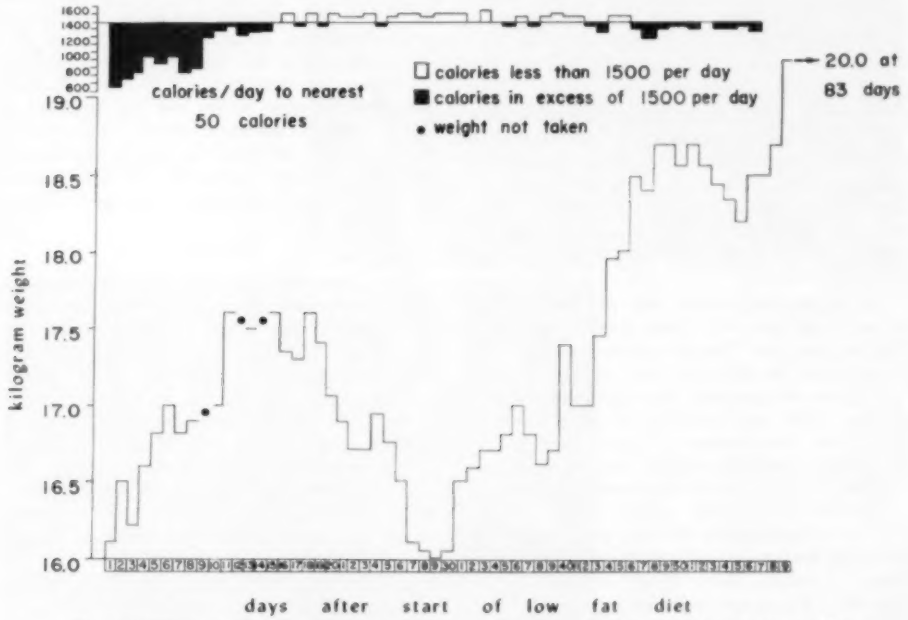


Fig. 4.—Effect of dietary treatment of patient with chylous ascites and lymphedema. Note initial gain in weight followed by spontaneous weight loss between 20 and 30 days after initiation of the diet. This was associated with increase in total serum proteins, decrease in size of the edematous extremities, and reduction in abdominal circumference. She then began to gain weight, which seemed to be due partially to accumulation of solid tissue rather than chylous fluid or edema.

rated fatty acids. Her skin became thickened and dry, with scaling in small patches. Her hair became coarse, lusterless, and sparse.

The purpose of this admission was to treat the possible deficiency with linoleic acid and to determine whether this essential fatty acid would be modified when it crossed from the intestine into the chyle. She was given a single feeding of 10 gm. of ethyl linoleate, 1 gm. of bovine serum albumin, and 40 gm. of dextrose. Samples of blood and chyle obtained before and at varying intervals after the feeding were analyzed for these substances and for the other polyunsaturated fatty acids. There was no significant or consistent change in the total amounts or patterns of unsaturated fatty acids in the blood or in the chyle. The bovine serum albumin was detected immunochemically in the blood but not in the chyle. Simultaneous blood and dextrose tolerance tests were almost identical with those obtained on the first University Hospitals hospitalization. There was no change in the fatty acid composition of the abdominal skin, as measured in biopsied specimens obtained before and two weeks after the test feeding.

During this hospitalization, the patient's respiratory capacity was evaluated. Her respiratory rate was 48 to 50 times per minute, with a tidal volume of 75 to 80 ml. and a maximum vital capacity of 250 ml. An effort was made to encourage deep breathing by giving her several toys that are activated by forceful blowing.

Outpatient Care.—Over the next months, she was seen at weekly intervals and required only an occasional paracentesis. Despite her unremitting abdominal distention, she was able to increase her tidal volume 130 to 150 ml. With this, her respiratory rate decreased to 24 to 28 times per minute. Her maximum vital capacity and minute volume remained constant.

During the three months after the single feeding of ethyl linoleate, there were marked changes in her skin and hair. The skin texture became normal except over the edematous arm and leg. Dryness and scaling disappeared. Her hair became fine in texture, silky, and considerably more abundant. In addition, she appeared to become more resistant to recurrent infection, staying well on several occasions when the rest of the family became ill.

On Jan. 3, 1957, her height, weight, and the several circumferences of her arms, legs, and abdomen were compared with these measurements taken 10 months earlier, at the start of the low fat diet. Her weight had increased from 18.9 to 25.9 kg. and her height from 33.75 in. to 35.75 in.; the maximum abdominal circumference from 69 to 83.5, the chest from 53 to 53.5, the edematous left foot, calf, and leg from 19.5 to 21, 31 to 38, and 31 to 31 cm., respectively; the edematous right hand, forearm, and upper arm from 21 to 27, 22 to 24.5, and 16 to 21 cm., respectively. Other significant increases were found only in the normal right calf and thigh. These were 15.5 to 17.5 and 18 to 23.5 cm. each. Later, because of progressive abdominal distention and the necessity for repeated paracentesis despite improved dietary management, it was decided to return intravenously a portion of the chyle obtained by each paracentesis in order to augment her nutrition and to minimize the total losses of protein and other substances in the chyle. Between Jan. 11, 1957, and June 10, 1957, twenty paracenteses were done at intervals of one or, occasionally, two weeks. Each time 600 to 650 ml. of the chyle were returned via a superficial abdominal vein. The chyle was drawn directly into a "Plasma-Vac" bottle through disposable Steri-Donor blood-drawing sets. The venipuncture needle was used for the abdominal puncture. The fluid was removed in a few minutes and given intravenously over 60 to 90 minutes. For about six to eight hours after each infusion, she would experience marked urinary frequency. No other complications of this therapy were observed.

All this time she continued to be active, outgoing, and purposeful, as she had become when the low-fat, high-protein, high-caloric diet was begun, and she had no illnesses. On June 4, 1957, she was given γ-globulin because of exposure to measles two days earlier. On June 17, the day before readmission for further diagnostic studies, she died in her sleep at about 10 a. m. She had been well the night before and had developed a slight cough in the early morning hours. Her sister who had also been exposed to measles had been having cough, photophobia, and conjunctivitis for two days and subsequently developed measles.

Autopsy

The subcutaneous fat measured only a centimeter in thickness but had a normal appearance. The thoracic cavity was small, and the lungs were compressed because of the extremely high diaphragm. There was no free fluid in the pleural spaces.

The abdominal cavity contained 12 liters of chylous material. This was sterile. The entire serosal surface of the abdominal cavity was covered by a shiny white plastic material measuring approximately 6 mm. in thickness. The mesentery of the small bowel could not be separated because of thick, tight adhesions. The entire mucosal surface of the small bowel was covered by collections of fatty material. Careful dissection of the mesentery failed to reveal lymphatic channels or lymph nodes. A thoracic duct of small caliber was located in the upper thorax but could not be traced below the 10th thoracic vertebra. The cisterna chyli was not found.

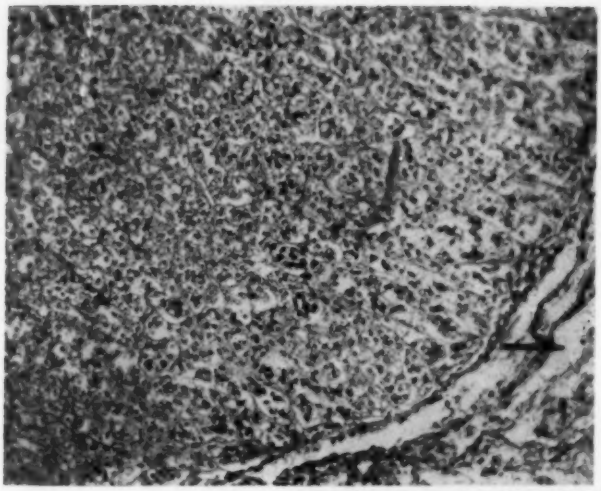


Fig. 5.—Section of adrenal gland showing dilated lymphatics in capsule (arrows). Hematoxylin and eosin; × 100.

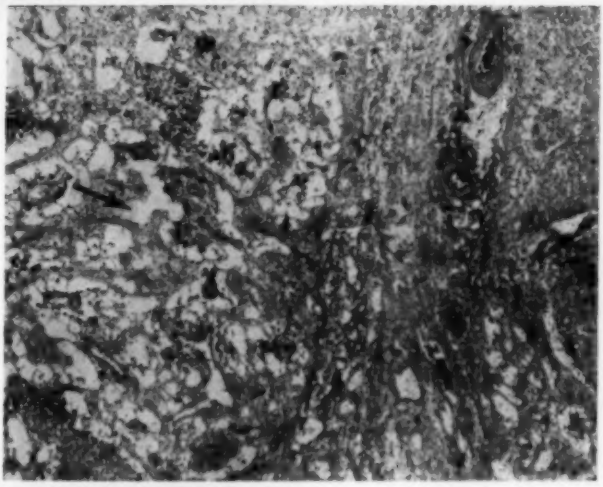


Fig. 6.—Medullary portion of the lymph node showing dilated lymphatic sinusoids. Hematoxylin and eosin; × 50.

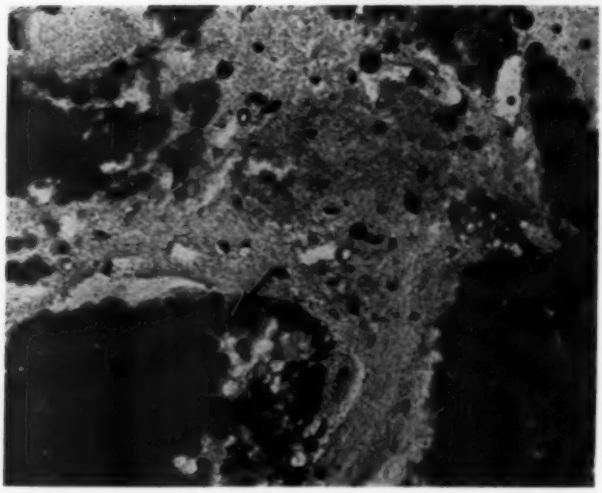


Fig. 7.—Mucosal surface of the ileum, fresh tissue stained with Sudan III, showing marked accumulations of fatty material in the intervillous spaces. × 25.

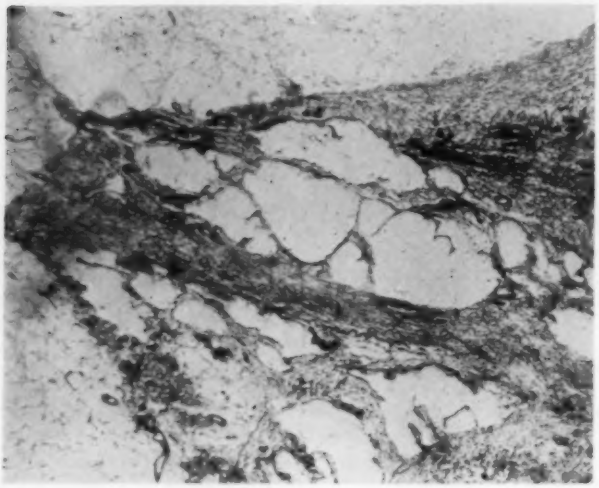


Fig. 8.—Cross section of the serosal surface of the ileum showing markedly dilated lymphatic channels (lacteals). It is apparently from these dilated channels which did not communicate with a collecting lymphatic system that chylous ascites arose. Hematoxylin and eosin; × 50.

Microscopic sections of the lungs revealed extensive areas of bronchopneumonia with peribronchiolar infiltration by polymorphonuclear and mononuclear cells. Sections of the liver showed a large amount of fibrous tissue in the portal areas. Dilated lymphatic channels were present in the connective tissue of the adrenals, skin, lymph nodes, kidneys, and spleen. This phenomenon was most marked in the adrenals and lymph nodes, where large, thin-walled lymph spaces widely separated other structures (Figs. 5 and 6).

Sudan stains of the mucosal surface of the ileum indicate the large amount of fat on the intestinal surface, as shown in Figure 7. Dilated lymphatic channels are shown on cross section of the intestinal serosa at its junction with the mesentery in Figure 8. These sections from fresh material confirm that the proximal lymph channels were filled with fatty material absorbed from the intestine. Once absorbed, the lymph with its lipid material escaped directly into the peritoneal cavity, since the normal avenues for lymphatic drainage were congenitally absent.

Comment

1. *The Syndrome.*—The four cases of chylous ascites and elephantiasis recorded in the literature and the case herein presented are summarized in Table 3. In all cases, the lymphedema was noted at birth but the ascites was not apparent until 2 to 10 months later. Perhaps the limitation of fat absorption present in the newborn and young infant permitted collateral lymphatics to transport the smaller amounts of chyle produced at that age away from the peritoneal cavity. In all cases the chylous ascites was the principal cause of morbidity, and in Cases 4 and 5 it was a significant factor contributing to death. In these later cases, massive weight gain with progressive ascites requiring multiple paracenteses, failure to grow in stature, dermatitis, and repeated respiratory infections characterized the clinical courses. In these two cases, no abdominal lymphatics were noted during exploratory laparotomy or at autopsy.

Of the three survivors, one was entirely well at the age of 10 months, the second recovered from the ascites during the 2nd year but had persistent edema at 15 years, and the third had persistent edema and ascites at the age of 6 years.

The cause and pathogenesis of this syndrome are obscure. However, the defect appears to result from a congenital anomaly, maldevelopment of the lymphatic system. The anlage of the lymphatic system forms in definite centers from which lymph vessels spread outward to vascularize and drain neighboring areas, from the jugular area to the tissues of the neck, head, and arms and from the pelvis to the legs and tissues of the pelvis and buttock. Two retroperitoneal centers form, one of which drains the

TABLE 3.—*Patients with Lymphedema and Chylous Ascites*

Author	Sex	Edema			Ascites		Clinical Course
		Age at Onset	Location	Duration	Age at Onset	Surgical Treatment	
Blume[1]							
Case 1	Male	Birth	Both feet	10 mo.	2 mo.	Laparotomy at age 2 mo., with finding of chylous ascites, temporary improvement	2 recurrences of chylous ascites & anasarca, with recovery by multiple paracenteses, recovery at age 10 mo.
Case 2	Male	Birth	Right arm	Persistent at age 15 yr.	During 1st yr.	Laparotomy during 1st yr. revealed chylous ascites & peritoneal lymph glands in blocks the size of walnuts	Persistent ascites treated by several paracenteses with cure
Southby[4]	Male	Birth	Right arm, left leg	Persistent at age 4 yr.	During 1st yr.	Laparotomy at 9 mo., with findings of small nodules over mesentery and small bowel, but no cause found	At 6 yr.; well but at times has recurrent ascites requiring paracentesis
McKendry[5]	Female	Birth	Right arm, left leg	Persistent to death at 18 mo. Impaired lymphatic absorption & transport in involved leg	During 1st 3 mo.	Laparotomy at 15 mo., with findings of chylous ascites; some lymphatics on serosal surface of ileum were distended with fat; general thickening of the small bowel, cecum, ascending colon, & omentum; no lymphatics noted; no obstruction found	Marked eczema & recurrent upper respiratory infections; gradual increase in lymphedema & ascites; no improvement on low-fat diet; progressive ascites requiring multiple paracenteses; total 10.5 liters of fluid removed; treatment included compression bandages, diuretics, & infusion of plasma, blood, & salt-free albumin; worse after laparotomy; death from asthmatic crisis & pneumonia
Warwick	Female	Birth	Right arm, left leg	Persistent to death at 5 yr.	During 1st 10 mo.	Laparotomy at 10 mo. showed chylous ascites & dilated lacteals; no apparent cause found; no improvement from surgery; laparotomy & thoracotomy & saphenous vein-peritoneal anastomosis done at 27 mo.; thoracic duct patent to diaphragmatic crura, no cisterna chyli, no lymph channels or lymph nodes in mesentery; many dilated, fat-filled lacteals on surface of small bowel; thickened mesentery & peritoneal surfaces with a few adhesions; transient improvement	Dermatitis & recurrent upper respiratory infections until fed linoleic acid; improvement on low-fat diet, but multiple paracenteses needed until death; total of 233 liters ascitic fluid removed

alimentary tract, while the other forms the cisterna chyli. A series of small endothelial-lined spaces in the mesenchymal tissue about the dorsal aorta unite to form both right and left thoracic ducts. In some areas, the primitive embryonic veins develop into lymphatics. As these lymphatics grow both centripetally and centrifugally, connections are made between the distal cellular areas and the large lymphatic vessels which empty into the jugular vein. This process begins in the embryo and presumably is completed before birth.[4,5]

It seems probable that a specific injury to this system might occur which could cause arrest of development, retardation of development, excessive development, or any combination of these possibilities. The massive and persistent lymphedema observed in four of the cases is similar to that found in Milroy's disease, where lymphatic obstruction is the primary malformation. In two of the three cases with persistent ascites, no demonstrable lymphatics or lymph nodes were found in the abdominal mesentery. In the two cases with transient ascites, it is presumed that development of these abdominal lymphatics was slower than normal. Whether a factor or factors injurious to the lymphatic system would act over a short or long period of time is not known. However, the different responses of the abdominal and distal lymphatics indicate that these two groups of lymphatics may either be at different stages of formation when the injury occurs or that they have somewhat different natures making them differentially susceptible to the hypothetical noxious agent or event. The absence of other cases of ascites and/or lymphedema in the known relatives of these cases is presumptive evidence that this syndrome is not genetically determined.

2. *Observations After the Feeding of Linoleic Acid.*—While on the low-fat diet, the patient's skin became dry and scaly, her hair became thick, coarse, and sparse, and she developed eczematous lesions over her abdomen which would come and go without explanation. In addition, while on the low-fat diet she seemed to be prone to develop repeated upper respiratory infections and pneumonia. After receiving the 10 gm. of ethyl linoleate, a marked reversal of these signs occurred. Her skin became normal, soft, and smooth, except over the edematous arm and leg, and her hair became fine in texture, silky, and abundant. These changes were still present nine months later when she died.

These changes are not unlike those observed by Hansen[6] in fat-deficient puppies. Indeed, they might be compared with his observations on eczematoid dermatitis developing in human infants deprived of fatty acids and the improvement occurring in these subjects and in patients with infantile eczema upon feeding of unsaturated fatty acids. However, the remarkable exception here is that these changes took place without consistent changes in the concentration of the unsaturated fatty acids in the serum or ascitic fluid. The ranges of serum polyunsaturated fatty acids measured by alkaline isomerization[7] before and after feeding ethyl linoleate are compared in Table 4 with values found in normal adults allowed a free diet.[8] It is apparent that the individual and total polyunsaturated acids of the serum of our patient were extremely low. With

TABLE 4.—*Serum Polyunsaturated Fatty Acids in Patient Compared with Normal Adults*

	Fatty Acids, Mg/100 Ml. Serum					
	Hexaenes	Pentaenes	Tetraenes	Trienes	Dienes	Total
Patient, before linoleate	1.8-3.0	1.3-2.6	3.6-7.1	1.9-15.7	6.7-35.4	21.5-60.1
Patient, after linoleate	0.4-1.5	1.4-2.7	3.8-6.4	1.7-11.5	13.9-22.7	24.0-42.0
Normal adults, free diet	5.3±0.9	4.7±0.9	13.5±1.3	10.0±1.3	80.0±11	129.0±11

the exception of trienoic acid, which is largely of metabolic origin and tends to be high in essential fatty acid deficiency, even the maximum values for serum polyunsaturated acids in the patient were only half the average values found in normal adults. Samples of serum from the patient contained the lowest content of polyunsaturated acids ever encountered in human serum in this laboratory. No consistent trend was observed in the ratio of trienoic acid/tetraenoic acid as the result of the low-fat diet or the linoleate supplement. However, the ratio, which is less than unity for normal adults, ranged from 0.37 to 2.55 in our patient, with an average of 1.23.

No significant difference in the content of polyunsaturated acids in the skin was observed as the result of linoleate supplementation, but this is not surprising in the light of animal experimentation. The content of polyunsaturated acids in the skin biopsies was less than the limit of sensitivity of the method. The total polyunsaturated acids of the ascitic fluid ranged from 30.3 to 76.1 mg/100 ml. Ranges of the individual groups of polyunsaturated acids were 0.8 to 2.1 for hexaenes, 0.7 to 2.9 for pentaenes, 2.5 to 8.0 for tetraenes, 3.2 to 9.2 for trienes, and 21.6 to 53.9 for dienes. The ratio of trienes to tetraenes ranged from 0.61 to 2.92, with an average of 1.46.

From the observations made upon the skin and the chemical analyses of the serum polyunsaturated acids, it seems clear that the patient developed a deficiency in essential fatty acids as a consequence of the low-fat diet. It appears that the supplement of 10 gm. of ethyl linoleate was insufficient to cause a detectable change in the polyunsaturated acid pattern of either serum or ascitic fluid, although it did cause a change in the dermatitis. These observations indicate that linoleic acid is essential to the health of dermal tissue but that the requirement for this function is rather small compared to the requirement to maintain normal serum lipids.

The relative ease with which essential fatty acid deficiency can be induced in infants fed a low-fat diet, as indicated by this study and a recent report from Hansen's group,[9] stands in contrast to the observations by Brown et al.[10] that maintaining an adult on a low-fat diet for six months failed to induce dermal signs of deficiency. The discrepancy may be a function of age and a reduced requirement of essential fatty acids in the adult. Essential fatty acid deficiency has been found to be developed much more easily in weanling rats than in adults.[11] It, therefore, appears that the feeding of a fat-free or low-fat diet to a child may have more serious consequences than feeding the same diet to an adult.

The improved resistance to repeated infections may have been coincidental, but it suggests that the essential fatty acids may play a role in the body's specific or nonspecific immune mechanisms. Further studies of this point are indicated.

3. *The Low-Fat Diet.*—The diet was devised to provide the patient with her caloric requirement for her "dry" weight (1,350 calories) plus 10% more to make up for her severe nutritional deficiencies. Because of the marked reduction in the rate of chyle formation on the trial fat-free diet, this diet was formulated so that only 5% of the total calories were derived from fat. This amounted to less than 10 gm. of fat per day. It was felt that further reduction in fat content would make the diet unpalatable. She was given three times the usual daily dose of a proprietary pediatric vitamin preparation.

The first and most dramatic effect of the diet was a prolonged period of freedom from paracentesis. For 83 days she did well, despite a gradual accumulation of ascitic fluid until she developed pneumonia and a paracentesis was required to promote her recovery. This period is shown in detail in Figure 1. The weight loss between Days 20 and 30 was concurrent with a rise in the serum proteins from 4.1 to 4.9 gm. total and from 1.4 to 1.9 albumin. This and the

decrease in the size of the edematous arm and leg probably were the result of the increased osmolarity of the plasma, caused by the rise in serum albumin. This mobilization of ascitic and edema fluid continued until the osmolarity of these fluids was the same as that of the plasma. After that, the accumulation of chylous ascitic fluid and of edema continued for the rest of her life.

Two studies of nitrogen balance, done during that hospitalization, showed ratios of 1.63 and 1.59 gm. nitrogen ingested per gram of nitrogen excreted. The normal ratio for this age is 1.07 ($\pm$ 0.1) to 1. This clearly shows the marked anabolism which can occur when an adequate diet is given to a relatively starved patient.

Significant changes in the electrophoretic patterns were noted between the 36th and the 55th days on the diet (Table 2). Similar changes have been described by Choremis,[12] who found decreased serum albumin and increased α-1- and α-2-globulins in severe malnutrition and toxic illnesses. He found the extent of these changes to be proportional to the severity of the illness, as was the period of time required for a return to a normal pattern. That our patient's electrophoretic pattern continued to show moderate depression of the albumin and moderate elevation of α-2- and β-globulin suggests that her augmented nutrition, although vastly improved, was still biochemically inadequate.

Another measurement of her improved nutrition is found in her growth in height. At 10 months, her height was 31 in.; at 45 months, it was 33¾ in.; at 51 months, it was 33¾ in.; at 57 months, it was 35¾ in., and at 62 months, it was 36 in. Between 10 and 51 months, she grew only 2 in. as compared to 10 in. for the average girl. However, during the last 11 months of her life, while she was on the low-fat diet, she grew 2¼ in., which is normal for girls of her age. Her weight increased with the ascites and edema and could not be used to assess her physical growth.

With these measurements of improved nutrition came a new personality. The patient was transformed from a child who sat all day and who had to be carried from place to place to one who could play in the yard and the neighborhood with her siblings and friends. She could even climb stairs, although she could not walk down them because her abdomen blocked her view of the steps. She wore out a pair of shoes, and plans were being made to place her in kindergarten the following autumn when she died.

4. *The Blood Picture and Immunologic Studies.*—The patient's typical differential white blood count was 82% neutrophils, 14% lymphocytes, and 4% monocytes, eosinophils, and basophils. This hemogram is in marked contrast with the average of 42% to 55% neutrophils, 36% to 49% lymphocytes, and 7% monocytes for a child between 2 and 5 years old. This plus the absence of abdominal lymphatics and lymph nodes, the lymphedema of the right arm and left leg, and the repeated infections suggested the possibility of a concurrent defect in the immunologic system.

Direct evidence that the lymphatic glandular system was normal was the finding of a normal lymph node and a normal morphologic response to antigenic stimulation in another lymph node. Furthermore, circulating antibody levels developed promptly and to normal levels after the same antigenic stimulation in this patient and in immunologically normal controls. Despite the low number of circulating lymphocytes, these cells appeared at the usual time interval and in the usual numbers in studies of the inflammatory response to cutaneous scarification.

Rous[13] states that patients with chylous effusion exhibit a reduced lymphocyte count because of the reduced flow of lymph through the thoracic duct, which is the chief pathway for entrance of lymphocytes into the blood stream. This explanation is consistent with the anatomic findings.

Whatever the basis for the increased susceptibility to infection in this child, the

many infections continued to be a problem during most of her life, and her death was due to overwhelming pneumonia. Unfortunately, the studies of immunological capacity, serum protein distribution, inflammatory response of the skin to mechanical irritation, and phagocytic capacities of leukocytes revealed no definable abnormalities in defense mechanism. The failure to define the basis for the increased susceptibility to infection in this patient indicates only the inadequacy of present methods for evaluating capacity for resistance to infectious disease.

Summary

The syndrome of congenital chylous ascites and elephantiasis is presented with a detailed report of the fifth known case.

Special observations are made concerning fatty acid deficiency, the blood picture, immunologic factors, and the effects of diet on the patient reported and on chylous ascites in general.

402 Heart Hospital, University of Minnesota (14) (Dr. Good).

REFERENCES

1. Blume, C.: Über Ascites chylosus beim Saügling, seine Heilungsaussichten und seine Beziehung zur Elephantiasis, Kinderärztl. Praxis 6:345-347, 1935.

2. McKendry, J. B. J.; Lindsay, W. K., and Gerstein, M. C.: Congenital Defects of the Lymphatics in Infancy, Pediatrics 19:21-35, 1957.

3. Southby, R.: Personal communication to the authors.

4. McClure, C. F. W.: The Development of the Lymphatic System in the Light of the More Recent Investigations in the Field of Vasculogenesis, Anat. Rec. 9:563-579, 1915.

5. Balankura, N. K.: Development of the Mammalian Lymphatic System, Nature, London 168:196-197, 1951.

6. Hansen, A. E.: Essential Fatty Acids and Infant Nutrition, Pediatrics 21:494-501, 1958.

7. Holman, R. T., and Hayes, H.: Determination of Polyunsaturated Acids in Lipides of Plasma and Tissue, Anal. Chem. 30:1422-1425, 1958.

8. Holman, R. T.; Hayes, H.; Malmros, H., and Wigand, G.: Effects of Dietary Fat upon Plasma Polyunsaturated Acids, Proc. Soc. Exper. Biol. & Med. 96:705-709, 1957.

9. Hansen, A. E.; Adam, D. J. D.; Boelsche, A. N.; Haggard, M. E.; Wiese, H. F.; Pratt, E. L., and Hunter, V.: Manifestations of Fat Deficiency in Infants, Fed. Proc. 16:387, 1957.

10. Brown, W. R.; Hansen, A. E.; Burr, G. O., and McQuarrie, I.: Effects of Prolonged Use of Extremely Low-Fat Diet on an Adult Human Subject, J. Nutrition 16:511, 1938.

11. Aaes-Jørgensen, E.; Leppik, E. E.; Hayes, H. W., and Holman, R. T.: Essential Fatty Acid Deficiency: II. In Adult Rats, J. Nutrition 66: 245-259, 1958.

12. Choremis, C., and Moschidis, C.: Paper Electrophoresis of Serum Proteins in Infantile Toxicosis, Acta paediat. 45:24-31, 1956.

13. Rous, F. P.: An Inquiry into Some Mechanical Factors in the Production of Lymphocytosis, J. Exper. Med. 10:238-270, 1908.

Serum Proteins in Childhood Tuberculosis

CHARLOTTE MARKER ZITRIN, M.D.; EDITH M. LINCOLN, M.D.; ROSARIO CARRETERO, M.D., and ENRIQUETA MELLY, M.D., New York

A good laboratory test, which can help establish the diagnosis and evaluate the activity of tuberculous disease, would be of inestimable value in the management of the tuberculous patient. With the advent of antimicrobial therapy, we need the additional service of an indicator to help the clinician decide when to treat and for how long. Ideally, one would strive for a test which is specific for the disease. Unfortunately, this ideal still eludes us. The hemagglutination test,[1] which appeared to hold such great promise initially, has been scrutinized again, recently, by Hirsch and associates,[2] in a group of patients followed with meticulous care. This study confirmed previous observations that there was no correlation between activity of tuberculous disease and hemagglutination titers.

In lieu of specific tests, then, can we get the required information from other sources? There have been several studies on the change of the serum γ-globulin in tuberculosis[3-7] which indicate that this component of the blood is increased in tuberculosis in proportion to the severity of the disease. Exceptions to this rule have occurred in patients either moribund or desperately ill with meningitis or miliary tuberculosis. In these instances, the γ-globulin may be relatively depressed.

Another change which occurs in the course of tuberculous infection is the increase in the serum α_2-globulin. Seibert and associates[8] showed, by means of electrophoresis, that the α_2-globulin was increased in adults with moderately and far advanced tuberculosis, and with carcinoma. She found that the α_2 is accompanied by a complex polysaccharide which, spectral absorption curves suggest, is probably a mixture of desoxyribonucleic acid, ribose, and derivatives of both. She and her associates[9] devised a simple chemical test, called the tryptophane-acid reaction, which measures this polysaccharide and, therefore, indirectly, the α_2-globulin. Increases in the α_2-globulin are attributed by her to tissue destruction, with the consequent release of such products of cellular disintegration as this complex polysaccharide.

In a recent study of experimental tuberculosis in guinea pigs by Sher and associates,[10] a comparison of serum protein changes by means of paper electrophoresis and turbidimetric techniques showed close agreement between the two methods. As in the previous studies on humans, the most conspicuous elevation was of the γ-globulin. In addition, the mucoprotein was elevated and the albumin decreased.

We have attempted to study the serum α_2- and γ-globulins of children with tuberculosis at monthly intervals, in order to determine whether this might help in the total evaluation of the patient. We wished to learn, first, the relation between α_2- and γ-globulin levels and severity of tuberculous infection; second, the effect of improvement or worsening of the disease on the blood

Submitted for publication Jan. 22, 1959.

This study was supported by Research Grant E-1281 from the Institute of Allergy and Infectious Diseases, National Institutes of Health, U. S. Public Health Service.

From the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University College of Medicine, Assistant Clinical Professor, Department of Pediatrics (Dr. Zitrin); Adjunct Professor, Department of Pediatrics (Dr. Lincoln); Research Fellows, Department of Pediatrics (Drs. Carretero and Melly). Present address of Dr. Zitrin, Hillside Hospital, 75-59 263d St., Glen Oaks, N. Y.

TABLE 1.—*Initial α_2- and γ-Globulins in Children with Tuberculosis*

Type of Tuberculosis	No. Cases	Range		Mean *	
		α_2	γ	α_2 (TA)	γ (KU)
Nontuberculous	22	32-62	5.0-16.4	46.0±9.4	10.9±3.7
Mantoux positive — tuberculosis observation	2	42-46	10.5-11.9	44.0	11.2
Healing or healed primary tuberculosis	9	42-65	4.9-15.2	59.0±13.1	10.1±3.6
Primary pulmonary — active					
Negative cultures	32	39-104	4.2-21.0	66.0±19.5	12.4±4.5
Positive cultures	42	45-117	7.5-36.0	78.0±18.3	16.6±6.8
Serous surfaces	10	48-110	12.9-42.3	86.0±22.4	19.6±8.6
Tuberculous adenitis	7	62-100	14.7-22.8	76.6±15.2	19.2±5.1
Pulmonary with local dissemination and cavity	3	83-143	15.4-34.8	103.0	23.2
Bronchogenic dissemination	1	—	—	143.0	31.0
Hematogenous dissemination	3	56-98	22.3-33.8	75.7	29.7
Serous meningitis	1	—	—	57.0	20.6
Miliary tuberculosis	12	58-99	8.4-23.8	80.4±12.6	15.4±5.6
Tuberculous meningitis	8	50-125	5.0-12.9	86.9±21.2	8.3±2.8

* The mean and standard deviation are given.

proteins; third, the effect of complications; and, fourth, the effect of drug therapy.

Method

The subjects of this study were 130 children between the ages of 3 months and 13 years, all patients on the children's tuberculosis service of Bellevue Hospital.

Blood was drawn soon after the patient was admitted to the hospital and examined for total protein, albumin, globulin, γ-globulin, α_2-globulin, and thymol turbidity. ESR and complete blood count were also done. These determinations were repeated at monthly intervals, as far as possible, during the patient's hospital stay. Clinical evaluation of the patients was made without prior knowledge of the results of laboratory determinations. The α_2-globulin was determined by means of the tryptophane-acid reaction (TA) devised by Seibert [9] and the values are expressed in terms of Klett readings. The γ-globulin was measured by the Kunkel zinc sulfate turbidity method [11] and the values expressed in Kunkel units (KU). The ESR was determined by the Wintrobe method.[12]

Results

Table 1 gives the initial values of the α_2- and γ-globulins, taken soon after the patient was admitted to the hospital for tuberculosis. Both globulin fractions were found to be increased in proportion to the severity of disease, except in miliary tuberculosis and tuberculous meningitis. Thus children with uncomplicated primary tuberculosis showed lower values than those with dissemination of their tuberculous disease.

Of the children with miliary tuberculosis, six had initially elevated γ-globulin values, while the others showed a gamma in the normal range. The α_2-globulin was moderately elevated, in comparison to marked

TABLE 2.—*Initial Serum Protein and Thymol Turbidity: Mean Values*

Type of Tuberculosis	No. Cases	Total Protein	Albumin/ Globulin	Thymol Turbidity
Mantoux positive — tuberculosis observation	2	7.5	4.7/2.9	4.2
Healing or healed primary tuberculosis	9	7.2	4.5/2.9	2.6
Primary pulmonary — active				
Negative cultures	32	7.6	4.6/3.0	5.6
Positive cultures	42	7.6	4.7/3.0	7.1
Serous surfaces	10	7.7	4.5/3.1	7.8
Tuberculous adenitis	7	7.6	4.6/2.9	8.6
Pulmonary with local dissemination and cavity	3	8.8	4.9/3.8	8.2
Bronchogenic dissemination	1	10.4	4.5/5.9	8.8
Hematogenous dissemination	3	8.5	4.3/4.2	14.5
Serous meningitis	1	8.2	5.0/3.2	10.4
Miliary tuberculosis	12	7.5	4.7/3.1	11.3
Tuberculous meningitis	8	7.5	4.7/2.8	5.1

elevation in the children with more chronic forms of dissemination, such as local pulmonary, bronchogenic, and protracted hematogenous dissemination of the disease.

In meningitis, *all* of the previously untreated patients showed a comparatively low γ-globulin initially and a moderately elevated α_2-globulin.

Table 2 gives the values for the initial total protein, A/G, and thymol turbidity, all determined on the same sample of blood as the globulins. The patients with uncomplicated primary tuberculosis showed, with few exceptions, normal T. P. and A/G values. The patients with evidence of dissemination tended to have high T. P. and globulin values. The thymol turbidity values generally paralleled those of the γ-globulin, upon which they are dependent.[13] There was no correlation between ESR and severity of disease in these children.

Table 3 gives the γ-globulin values in infants under 18 months of age at the time of the determinations. Of the 25 infants included in the Table, 21 had abnormally high values. All but one of the children in the 3-9-month age group had high values (the low value occurring in an infant of 8½ months with miliary tuberculosis), although physiological hypogammaglobulinemia normally occurs during this period.

Figures 1 through 8 represent serial studies of the α_2- and γ-globulins of those individual patients whom it was possible to follow for several months. The ordinate expresses the values for the globulin fractions, the abscissa time in months. Specific therapy is indicated just below each graph.

TABLE 3.—*γ-Globulin in Children Under Eighteen Months of Age with Tuberculosis*

Age, Mo.	No. of Patients	γ-Globulin	
		Range	Mean
0-3	0	—	—
3-6	5	18.7-33.0	23.0
6-9	5	9.9-24.9	20.6
9-12	10	9.4-36.0	19.3
12-15	3	8.4-16.5	12.3
15-18	2	14.8-21.0	17.9

(The drug abbreviations used are as follows: INH=isoniazid; SM=streptomycin; PAS=aminosalicylic [para-aminosalicylic acid]). Other pertinent information, such as the results of cultures for acid-fast bacilli and occurrence of complications, tuberculous or nontuberculous, has been inserted onto each graph. The patients showed progressive clinical and x-ray improvement unless otherwise noted on the graphs.*

* It is not possible, for various reasons, to follow all of the patients for prolonged periods. Those with minimal or healing tuberculosis were hospitalized for a relatively short time. Among the other children with uncomplicated primary tuberculosis, some were included in a Public Health Service series to determine the effect of treatment on prevention of tuberculous meningitis. We have, as yet, no knowledge of the treatment or nontreatment of this group. Since we are unable to evaluate the effect of treatment on the blood proteins of these patients, we have not included their serial graphs in this paper.

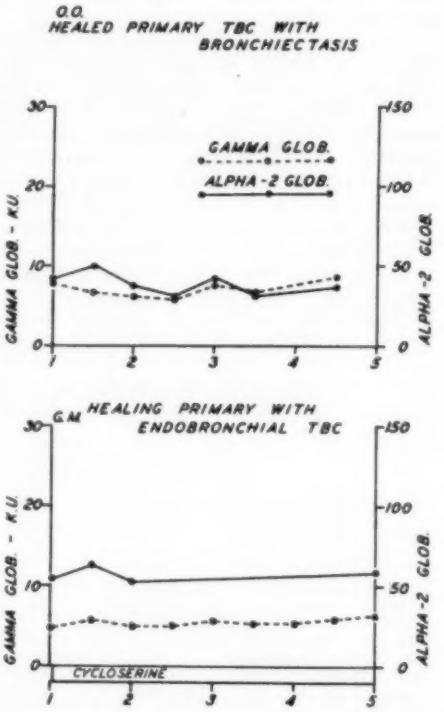


Figure 1

Figure 1 illustrates one patient with healed and one with healing primary tuberculosis. The curves for both globulin fractions are flat, always within the normal range.

Figure 2 shows the results obtained with seven patients who had uncomplicated primary tuberculosis and were treated with specific antimicrobial drugs. In each instance, there was an initial elevation of the γ-globulin. This returned to normal in 1.5 to 3 months after the onset of therapy, with a mean time of 2.2 months. In six of the seven children, the α_2 also was elevated initially. It returned to normal in 1 to 3 months after the onset of therapy (mean of 2.3 months).

Figure 3 represents serial studies on three patients admitted to the hospital with asymptomatic primary tuberculosis who were *not* treated with antituberculous drugs and developed various complications during their

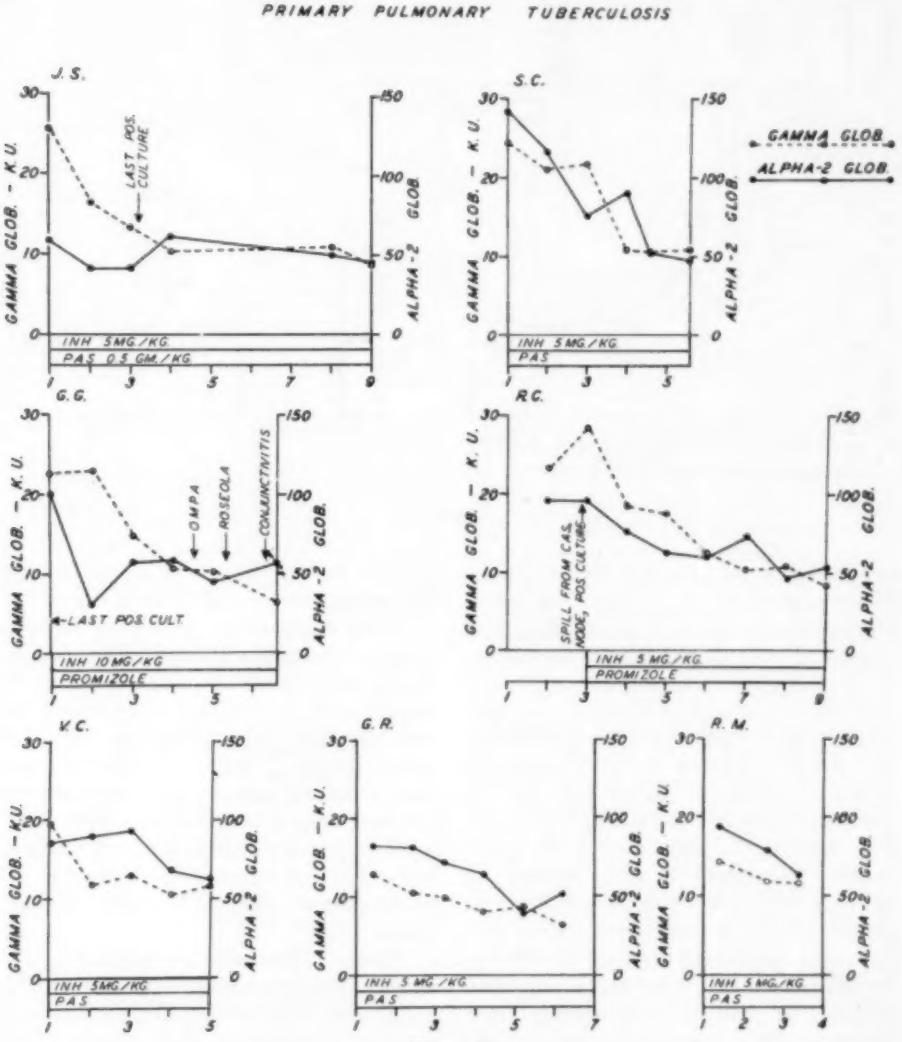


Figure 2

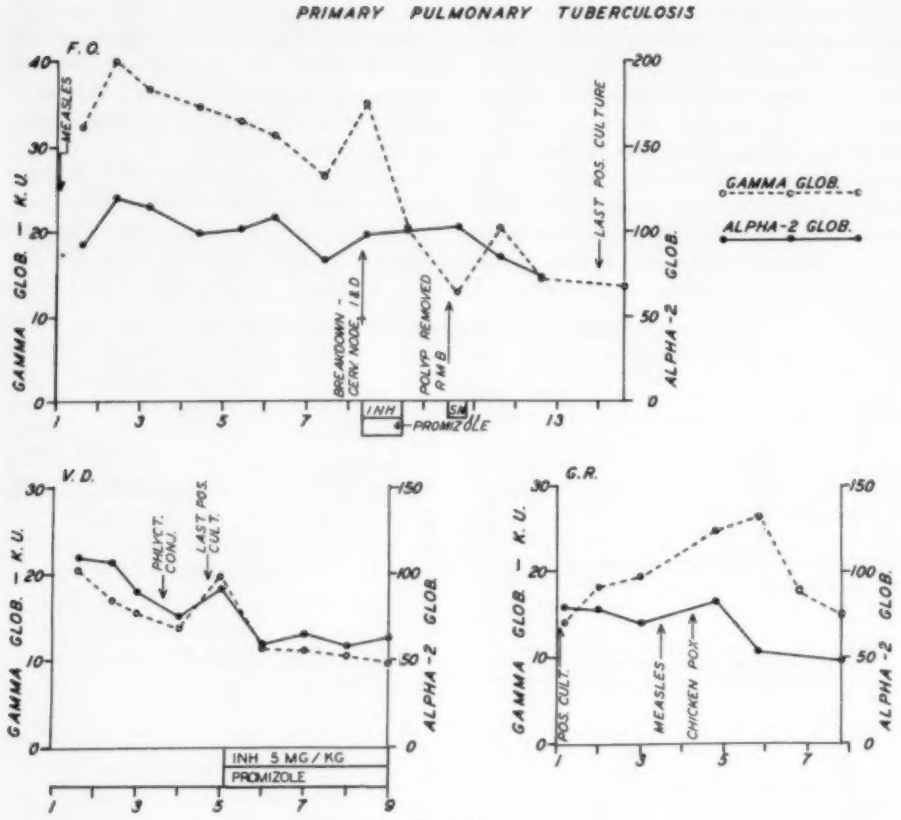


Figure 3

hospitalization, as indicated on the graphs. In the case of F. O., a very short period of specific therapy was given after eight months of observation, and, in the case of V. D., antituberculous therapy was begun after five months of observation. In these children, the γ-globulin was elevated initially and remained elevated for 10½, 6, and 7½ months. The α_2, at a lower level than the γ-globulin in two of the children, nevertheless remained elevated for 12, 5, and 5 months, respectively, in these patients. In the child V. D., the drop to normal of the two globulin fractions occurred shortly after the onset of specific therapy. In the untreated patient G. R., the course was complicated by measles and chicken pox. Following these complications, there was a marked rise in the γ, which persisted for two months, and a slight rise in the α_2.

Figure 4 represents three cases of more serious tuberculous disease. The globulin curves are similar to those seen in the treated cases of primary tuberculosis, except that the initial values are somewhat higher, (mean γ of 28.2 compared to mean of 20.6 for the patients with uncomplicated primary tuberculosis) and they take somewhat longer to return to normal (two normal after four months, two lower but still above normal after eight months of therapy).

Figure 5 illustrates the globulin picture in two children who developed pleural effusions while under observation for untreated primary tuberculosis. Both showed a rise

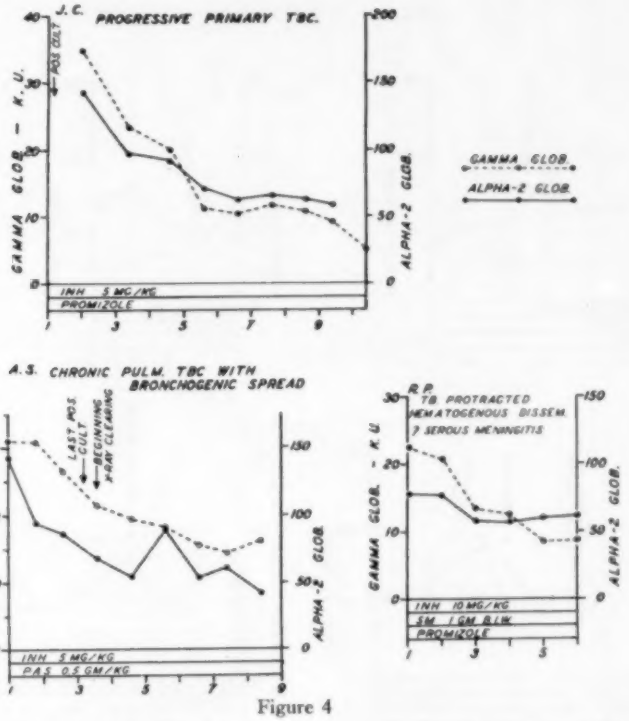


Figure 4

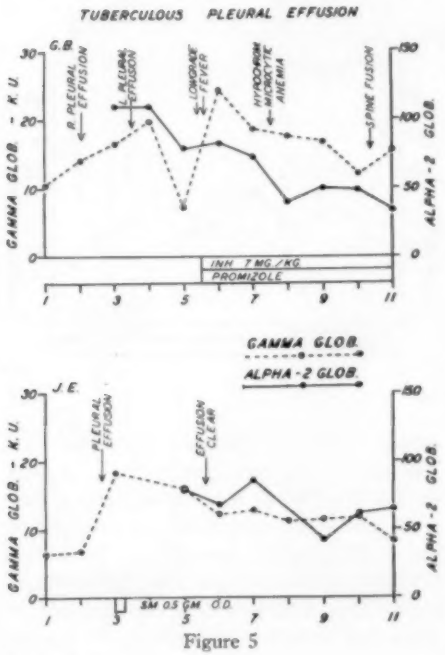


Figure 5

in the γ following the effusion. The α_2-globulin was also elevated at that time. In G. B., the picture was complicated further by tuberculosis of the vertebral column. After the onset of therapy, both his γ- and α_2-globulin gradually returned to normal. J. E. did not receive any specific therapy. However, after his effusion cleared, the γ-globulin became normal and remained so for the rest of his hospitalization. The α_2 returned more slowly to normal.

Figure 6 illustrates the serial pattern in six children with miliary tuberculosis. Both globulin fractions were elevated initially, the γ-globulin to a greater degree than the α_2. Under therapy, three showed a gradual decline, and three, after an initial rise in the gamma, then declined gradually to normal levels. In C. M., the picture was complicated by measles and chicken pox. Both globulin curves rose sharply during this period. Mumps, in the case of I. P., was not followed by any rise in the globulin values.

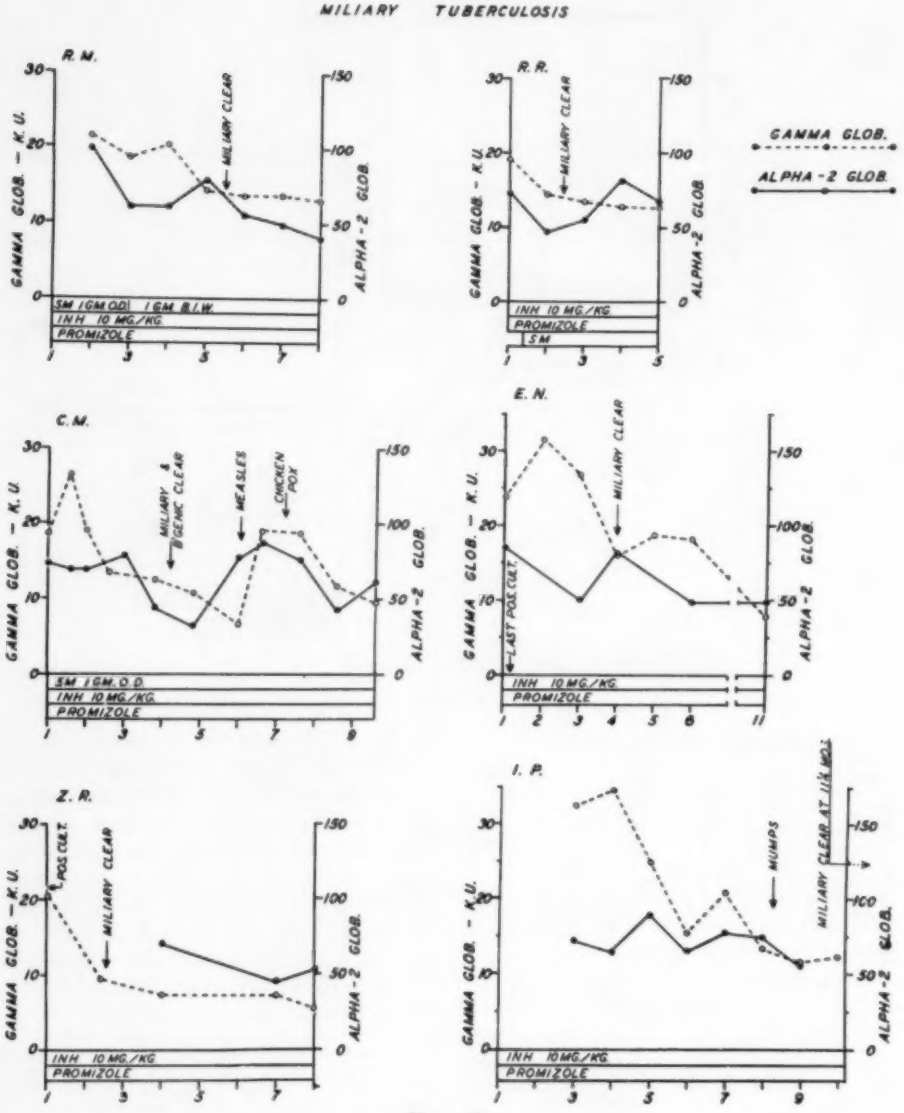


Figure 6

Figure 7 shows four children with miliary tuberculosis whose curves resemble those of the children with tuberculous meningitis (Fig. 8), that is, with initially relatively low γ-globulin and high α_2. Two of these children developed hypogammaglobulinemia. One of them, D. M., reached low levels of 1.6 and 1.8 KU. His γ-globulin finally returned to normal after one year. This child was one of our most seriously ill patients, with Pott's disease, tuberculous cervical adenitis, and positive urine culture complicating the miliary disease. In addition, he became resistant to isoniazid, and only after streptomycin was added to the regimen did he show any clinical improvement. W. P. also

MILIARY TUBERCULOSIS

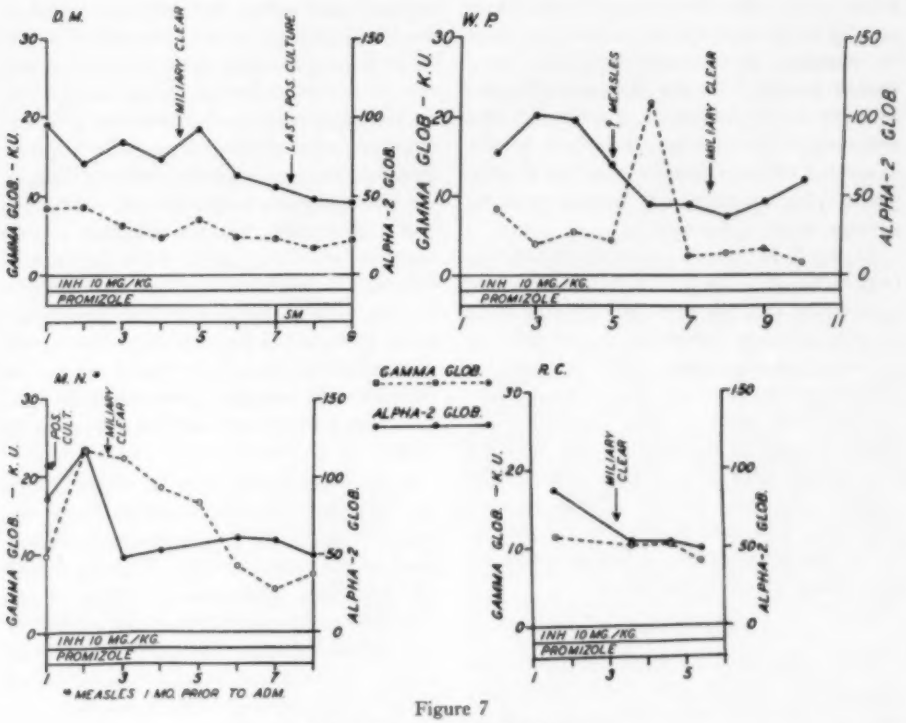


Figure 7

TUBERCULOUS MENINGITIS

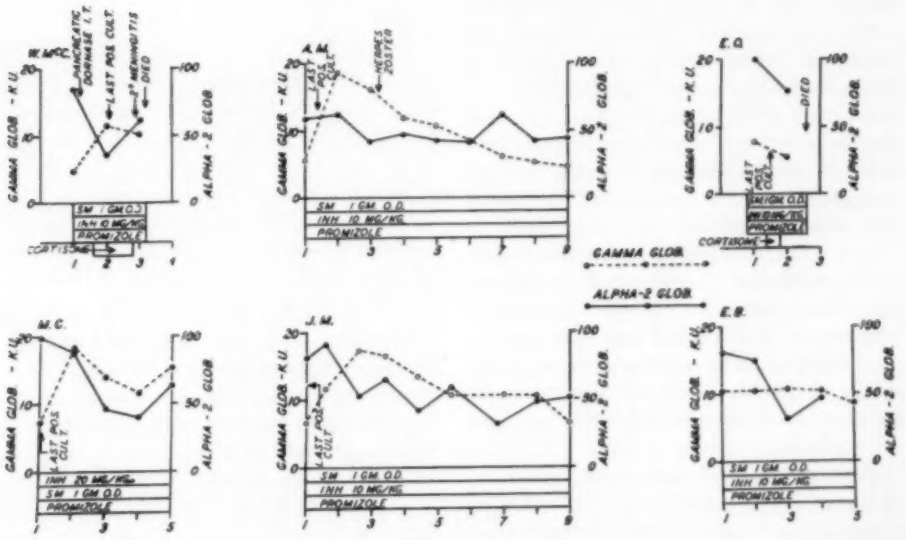


Figure 8

reached a low point of 1.6 KU in his γ-globulin level. This child had very slow clearing of his miliary lesions. They did not disappear by x-ray until 25 weeks after the onset of treatment, an unusually long time for a treated patient. In the Bellevue Hospital series,[14] for example, it was found that complete x-ray clearing of miliary lesions in treated children usually occurred 8 to 16 weeks after therapy was begun, with an average time of 13 weeks.

Figure 8 illustrates six cases of tuberculous meningitis. In all of these, the initial α_2-globulin was elevated and the γ-globulin ranged from low to normal. As the children improved, the α_2 dropped. In three of the four cases who survived, the γ rose to levels greater than normal, then gradually declined. In one of the children who survived and in two who died of their disease, the γ never rose above normal. The α_2 showed, in general, a gradual decline. In one patient, A. M., the complication of herpes zoster did not appear to affect the curve.

Comment

It is important to keep in mind that tuberculosis in children is a complex disease with an enormous range of activity and severity. In the most benign form, uncomplicated primary tuberculosis, most of the children are entirely asymptomatic and are picked up as the result of routine chest x-ray or tuberculin test. In Lincoln's series,[15] over 85% of the children admitted with primary tuberculosis were diagnosed as a result of case-finding methods, usually through history of contact with a known case or by routine tuberculin test.

In any group collected by means of case-finding methods, a substantial percentage can be expected to have minimal disease, as indicated by their clinical course, x-ray picture, and absence of positive cultures, while others, according to these same criteria, exhibit varying degrees of severity and take correspondingly longer to heal.

With a disease of such great variability, one must expect a similarly wide range of results in any test, specific or nonspecific. There is such a range in the α_2- and γ-globulin values. Nevertheless, if we follow the mean of each group, we find that there is a definite increase in proportion to the severity of disease for both globulin fractions, except in miliary tuberculosis and meningitis, which will be discussed separately. For example, in primary tuberculosis with negative cultures, the group with minimal disease, we find a greater proportion of normal initial values and a lower mean than in primary tuberculosis with positive cultures (Table 1). With the occurrence of complications, such as involvement of serous surfaces (pleurisy or peritonitis), adenitis, and dissemination of various types, *all* of the patients had initially elevated γ-globulin values and most had elevated α_2 values as well.

It is of interest to note, in Table 3, that the infants with tuberculous infection showed rises in the γ-globulin comparable to those in the older children. The physiological hypogammaglobulinemia which occurs normally in infancy [16,17] was not evident in any of these patients. Indeed, in this small group, the younger infants had a higher mean value for γ-globulin than the older ones, but this is probably a reflection of the greater severity of disease in the younger patients.

If there is a relationship between the globulins and tuberculous disease, one would expect to see a decrease with improvement, more rapid if specific antimicrobial therapy is given, and an increase with worsening or development of a complication. We attempted to follow the proteins at monthly intervals in order to get serial studies of the patients and determine, if possible, how the course of the disease affected the proteins.

In Figure 2, all of the patients had uncomplicated primary tuberculosis and were treated with specific antituberculous drugs. In each instance, there was a gradual but definite decrease in the values of both α_2- and γ-globulins as the patient improved. Most of the children in this group had rather high initial values, which makes the

subsequent decline fairly dramatic. G. R. and R. M., who had only slightly elevated initial values, naturally have flatter curves. It is of interest to note that J. S., whose initial value for γ-globulin was 25.8 KU, was only 3 months old at the time.

The three children with more serious tuberculous disease shown in Figure 4 were treated because of the severity of their infection. The clinical course, in each instance, although initially stormy, was one of gradual improvement and the decrease in blood globulins parallels the clinical improvement.

In contrast to the above, Figure 3 illustrates the course of the globulin fractions in three children hospitalized with asymptomatic primary tuberculosis who were not treated and developed complications during their course. Their globulin curves remained abnormal for much longer periods of time than those of the treated patients, including those with miliary tuberculosis and meningitis. The two patients with pleural effusion, shown in Figure 5, also were untreated. They, too, had prolonged elevations of the globulin fractions.

This is admittedly a small group, but it suggests that the γ-globulin returns to normal more quickly with specific treatment. It is known that some children who are treated with isoniazid become negative tuberculin reactors. Presumably, that is due to the disappearance of antibody in the host. Similarly, the drugs, by decreasing the antigen, may effect a corresponding decrease in production of *humoral* antibody, therefore a decrease in the γ-globulin.

Effect of Complications.—The charts show that, in the children who had an uncomplicated course, there was a gradual decrease in the α_2- and γ-globulins. Time and again, however, we saw a rise in the γ, less often in the α_2, with the development of a complication. For example, in the case of F. O., this was seen following the breakdown of a tuberculous cervical node and, later, removal of a polyp from the right main bronchus. In G. B. and J. E., a rise followed pleural effusion, and in R. C. it followed a spill from a caseous node. The curve in the patient G. B. suggests that such an increase may precede clinical evidence of a complication. This possibility was suggested also by the curve of a patient reported in a previous paper.[7] More frequent determinations at, for instance, weekly intervals, would be necessary to evaluate this possibility.

In G. R. and C. M., there was a rise following measles and chicken pox and, in W. P., a rise following questionable measles (after γ-globulin prophylaxis). However, no rise occurred after herpes zoster in A. M., mumps in I. P., otitis, roseola, or acute nontuberculous conjunctivitis in G. G.

No effect was noted following numerous instances of upper respiratory infection. Similar findings were reported in detail in patients described previously.[7] This corresponds with our data on normal, nontuberculous children with acute respiratory infections, including upper respiratory infection, tracheobronchitis, bronchiolitis, bronchopneumonia and lobar pneumonia. Of 45 children studied, all had normal γ-globulin values but 4; these 4 had slightly elevated values, the highest being 16.7 KU.[19]

Miliary Tuberculosis.—Several of the children with miliary tuberculosis showed high initial globulin values, with a gradual return to normal during the course of therapy (Fig. 6). In general, these children had a good response to therapy and early clearing of their miliary lesions by x-ray. The α_2-globulin was moderately elevated, whereas in pulmonary disease with local or bronchogenic dissemination, there was marked elevation. If the increase in α_2 parallels tissue destruction, as Seibert and associates[9] and Shedlovsky and Scudder[18] suggest, then this difference is understandable on the basis that miliary disease, a much more acute form of tuberculosis, would be associated with less tissue destruction.

In contrast to the above group, five children with miliary disease had curves which showed a disparity between the α_2- and

γ-globulin (Fig. 7). Their curves were like those seen in meningitis rather than those of the other patients with miliary disease. In two of these children, the miliary process took an unusually long time to clear by x-ray (W. P. and D. F., the latter not illustrated on the chart). In another (D. M.) the disease was complicated by multiple tuberculous foci in the body and development of resistance to isoniazid. Before the days of chemotherapy, 90% of the children at Bellevue Hospital with miliary tuberculosis eventually developed tuberculous meningitis.[15] It is interesting, therefore, to speculate about whether these children, whose protein picture resembled that of the meningitis patients, may have been the ones most likely to develop meningitis if they had not been treated. Further studies on larger numbers of children may shed some light on this.

What is the explanation for the low γ-globulin seen in these children with tuberculous meningitis and miliary tuberculosis? Is the child more susceptible to these previously fatal forms of tuberculosis because he is less capable of producing antibodies than other persons or is it the severity of the infection which causes a depression of antibody formation in the host? The fact that, in several of the children with meningitis the low γ-globulin was relatively transient, rising to twice the normal values as the child improved, supports the latter view. Among the miliaries as a case in point, D. M. had a hypogammaglobulinemia during his active tuberculous infection, but one year later, the γ-globulin had returned to normal. This indicates that it was not a primary failure in the child but secondary to another factor, in this instance probably the effect of overwhelming infection.

As with any laboratory test, the results can only be used to supplement, not supplant, good clinical judgment. If used in this manner, it would appear that the principal value of determining the serum proteins lies in obtaining individual serial patterns. These can be used by the clinician as aids in following the progress of the patients. In children, their value in this regard is superior to the sedimentation rate. A sharp rise, especially in the γ-globulin, suggests the possibility of a complication. The worst prognostic sign appears to be elevated α_2- and relatively low γ-globulin.

Summary

In 130 children with primary tuberculosis or complications thereof, it was found that the serum α_2- and γ-globulins were increased in proportion to the increasing severity of the tuberculous infection. Exceptions to this occurred in all patients with tuberculous meningitis and 6 of the 12 patients with miliary tuberculosis, these showing an elevated α_2- and relatively low γ-globulin. This disparity, occurring in the sickest patients, was interpreted as being the worst prognostic sign.

In 33 patients followed at monthly intervals with serial studies of the globulins, the patients who were treated and had an uncomplicated course showed a gradual decrease in the two globulin fractions which appeared to parallel clinical improvement. In five untreated patients, three with primary tuberculosis and two with tuberculous pleurisy, the globulin fractions remained elevated much longer than in the treated patients of all degrees of severity, including most of the children with miliary tuberculosis and meningitis.

Tuberculous complications in these children were followed (or accompanied) by a rise in the γ-globulin and, to a slighter degree, the α_2-globulin. A similar rise was seen following measles and chicken pox, but no increase was noted following upper respiratory infections, acute otitis and other nontuberculous intercurrent infections.

There were no significant changes in the total protein or A/G in these children, except for two with marked, protracted tuberculous disease.

Hillside Hospital, 75-59 263d St., Glen Oaks, N. Y. (Dr. Zitrin).

REFERENCES

1. Middlebrook, G.: A Hemolytic Modification of the Hemagglutination Test for Antibodies

Against Tubercle Bacillus Antigen, J. Clin. Invest. 29:1480, 1950.

2. Hirsch, J. G.; Schaedler, R. W.; Pierce, C. H., and Smith, I. M.: A Study Comparing the Effects of Bed Rest and Physical Activity on Recovery from Pulmonary Tuberculosis, Am. Rev. Tuberc. 75:359, 1957.

3. Seibert, F. B., and Nelson, J. W.: Electrophoresis and Serum Proteins in Tuberculosis and Other Chronic Diseases, Am. Rev. Tuberc. 47: 66, 1943.

4. Volk, B. W.; Saifer, A.; Johnson, L. E., and Oreskes, I.: Electrophoretic and Chemical Serum Protein Fractions in Pulmonary Tuberculosis, Am. Rev. Tuberc. 67:299, 1953.

5. Levin, B. M.; Kaufman, H., and de la Huerga, J.: Gamma Globulin Studies in Tuberculosis in Children, A. M. A. Am. J. Dis. Child. 83:26, 1952.

6. Guillermand, J., and Groulade, J.: The Changes in Blood Proteins in the Course of Pulmonary Tuberculosis (in French), Rev. prat. 6: 3136, 1956.

7. Zitrin, C. M.; Lincoln, E. M.; Saifer, A., and Lewkowicz, S.: Serum Gamma Globulin in Childhood Tuberculosis, Am. Rev. Tuberc. 74:15, 1956.

8. Seibert, F. B.; Seibert, M. V.; Atno, A. J., and Campbell, H. W.: Variations in Protein and Polysaccharide Content of Sera in the Chronic Diseases, Tuberculosis, Sarcoidosis, and Carcinoma, J. Clin. Invest. 26:90, 1947.

9. Seibert, F. B.; Pfaff, M. L., and Seibert, M. V.: A Serum Polysaccharide in Tuberculosis and Carcinoma, Arch. Biochem. 18:279, 1948.

10. Sher, B. C.; Dubin, A.; Takimura, Y.; de la Huerga, J., and Popper, Hans: Serum Protein Changes in Experimental Tuberculosis, Am. Rev. Tuberc. 77:120, 1958.

11. Kunkel, H. G.; Ahrens, E. H., and Eisenmenger, W. J.: Application of Turbidimetric Methods for Estimation of Gamma Globulin and Total Lipid to the Study of Patients with Liver Disease, Gastroenterology, 11:499, 1948.

12. Wintrobe, M. M., and Landsberg, J. W.: A Standardized Technique for the Blood Sedimentation Test, Am. J. M. Sc. 189:102, 1935.

13. MacLagan, N. F.: Flocculation Tests: Chemical and Clinical Significance, Brit. M. J. 2:892, 1948.

14. Lincoln, E. M.: Miliary Tuberculosis in Children Treated with Antimicrobial Drugs, unpublished data.

15. Lincoln, E. M.: Course and Prognosis of Tuberculosis in Children, Am. J. Med. 9:623, 1950.

16. Orlandini, O.; Sass-Kortsak, A., and Ebbs, J. H.: Serum Gamma Globulin Levels in Normal Infants, Pediatrics 16:575, 1955.

17. Oberman, J. W.; Gregory, K. O.; Burke, F. G.; Ross, S., and Rice, E. C.: Electrophoretic Analysis of Serum Proteins in Infants and Children, N. England J. Med. 255:743, 1956.

18. Shedlovsky, T. S., and Scudder, J.: A Comparison of Erythrocyte Sedimentation Rates and Electrophoretic Patterns of Normal and Pathological Human Blood, J. Exper. Med. 75:119, 1942.

19. Zitrin, C. M., and Melly, E.: Serum Gamma Globulin Values in Children with Acute Infections, unpublished data.

Diabetes Mellitus or the Prediabetic State in the Mother and the Neonate

Effect on the Homeostasis of Calcium, Phosphorus, and Some Other Electrolytes in the Neonate on the First Day of Life

I. F. GITTLEMAN, M.D.; J. B. PINCUS, M.D.; E. SCHMERTZLER, B.S., and F. ANNECCHIARICO, Brooklyn

In a previous publication we noted that the incidence of hypocalcemia on the first day of life was significantly higher in infants born to mothers who had abnormal pregnancies, labor, or both.[1] In this group, diabetes mellitus in the mother played a prominent role.

We therefore investigated the incidence of hypocalcemia on the first day of life in infants born to diabetic mothers and to mothers who were found to have a prediabetic state during pregnancy.* We also made simultaneous observations on some other constituents of the blood.

Patient Material and Methods

The infants were divided into two groups. Group I consisted of 22 infants born to diabetic mothers whose diabetic state had been recognized for periods varying between 1 and 18 years. All mothers of this group of infants received insulin, but no other hormones. All but two infants were delivered by cesarean section. Group II contained 36 infants born to mothers who were considered by their obstetricians to be in the prediabetic state.* The mothers of the second group received no insulin, and the glycosuria was controlled by diet. In this group 23 infants were delivered by cesarean section and 13 per vias naturales. Mothers who were delivered by cesarean section received intravenous glucose during the operative procedure. Blood was obtained by venopuncture on the first day of life as soon after birth as was possible. The following blood constituents were measured: calcium and phosphorus in all infants; sodium, potassium, chloride, carbon dioxide, glucose, and hematocrit values in some.

The serum calcium and phosphorus determinations were done by the microchemical methods as described by A. Sobel et al.[2,3] Sodium values were obtained using the Perkin-Elmer flame photometer with 0.8 mg/ml. of lithium as internal standard.[4,5] The flame photometer was also used for potassium determination with 0.2 mg/ml. of lithium as internal standard; 0.05 ml. of nonhemolyzed serum was used for each determination. The CO_2 content was measured on 0.03 ml. of plasma by the use of the Kopp-Natelson gasometer.[6] The concentration of chloride was obtained by the ultramicro modification of the method of Schales and Schales on 0.01 ml. of nonhemolyzed plasma.[4,7,8] A modified micromodification of the Folin-Wu method was used for the estimation of glucose in the blood samples.[7,9] The hematocrit was read on blood samples contained in tubes sealed with wax, after they were centrifuged at a speed of 2,000 rpm for 15 minutes. The measurements were made in five tubes, and the average was taken.

Results

Table 1 summarizes the serum calcium and phosphorus levels in infants on the first day of life born to diabetic mothers. The type of delivery, the duration and control of the diabetes, and the symptoms that the infants exhibited are also presented. Of the 22 infants 6 had a hypocalcemia (27.3%). Sixteen infants born to mothers whose diabetes was adequately controlled had normocalcemia, ranging between

Submitted for publication Dec. 20, 1958.

Supported by U. S. Public Health Service Grant A-126 (C5)(C6) and Ross Laboratories, Columbus, Ohio.

From the Department of Pediatrics and Division of Biochemistry, The Jewish Hospital of Brooklyn, and the Department of Pediatrics, State University of New York College of Medicine, Downstate Medical Center.

*A mother was considered in the prediabetic state by the internist and obstetrician when her glucose tolerance curve was diabetic-like in one or more pregnancies.

TABLE 1.—*Type of Delivery, Duration and Degree of Control of Diabetes in the Mothers; Symptoms, Calcium and Phosphorus in Their Respective Infants*

Patient No.	Type of Delivery	Duration of Diabetes, Yr.	Degree of Control of Diabetes	Ca (Mg/100 Ml.) in the Infant at Birth	P (Mg/100 Ml.) in the Infant at Birth	Symptoms Observed in the Infant and Outcome
1	Cesarean section	8	Good	10.2	5.7	Edema; recovered
2	Cesarean section	1	Good	10.0	7.1	No untoward symptoms
3	Cesarean section	18	Good	10.0	—	Slight respiratory distress for a short while; recovered
4	Spontaneous	1	Good	9.6	4.9	Vomiting and distention on 2d day (meconium plug syndrome); recovered
5	Cesarean section	8	Fair	9.2	6.8	Edema; recovered
6	Cesarean section	6	Good	9.0	6.4	Edema; marked tremors; recovered
7	Cesarean section	10	Good	8.7	6.1	Weak cry on the first day; recovered
8	Cesarean section	1	Good	8.6	6.6	Edema, marked tremors on 2d day; recovered
9	Cesarean section	6	Good	8.6	8.0	Edema; recovered
10	Cesarean section	14	Good	8.4	7.5	Edema, cyanosis, periods of apnea and retractions for 2 days; recovered
11	Cesarean section	15	Good	8.4	5.5	Edema, jaundice on 3d day, lethargy; fed poorly; recovered
12	Cesarean section	1½	Good	8.2	7.6	Edema; recovered
13	Cesarean section	5	Good	8.2	5.5	Tremors on 3d day; recovered
14	Cesarean section	6	Fair	8.0	6.4	Edema, abdominal distention, grunt, and rapid respirations for 2 days; recovered
15	Cesarean section	3½	Good	8.0	—	Edema, tremors of extremities; recovered
16	Cesarean section	6	Fair	8.0	6.1	Edema, periods of apnea and cyanosis; rapid respirations for 1 day; recovered
17	Cesarean section	1	Good	7.0	5.7	Shallow respirations; recovered
18	Cesarean section	3-4	Poor	7.0	8.5	Edema, cyanosis, respiratory distress, irritability; recovered
19	Spontaneous	3	Good	6.5	6.1	Edema, mild cyanosis, convulsions on 2d day; recovered
20	Cesarean section	3	Poor	6.2	8.5	Edema, periodic cyanosis, respiratory distress for 2 days; recovered
21	Cesarean section	12	Good	6.0	5.8	Two hours after birth — cyanosis; shallow, rapid respirations; improved in 36 hours; recovered
22	Cesarean section	3	Poor	5.6	7.3	Edema, marked tachycardia, cyanosis, large liver; died; corticotropin administered to infant

8.0-10.2 mg/100 ml. Three infants born to mothers whose diabetic state was similarly under control had hypocalcemia, ranging between 6-7 mg/100 ml., while three infants whose mothers' diabetic state was poorly controlled also had hypocalcemia, ranging between 5.6-7 mg/100 ml. Out of the 16 normocalcemic infants, 11 had varying degrees of edema. Four in this group had tremors and four had respiratory symptoms. In the six hypocalcemic infants four were edematous, two had irritability and/or convulsions, and five had respiratory distress and/or periods of cyanosis. None of the infants who had normal calcium concentrations had any severe respiratory symptoms. While the symptoms overlapped, respiratory distress was always associated with calcium levels of about 8.0 mg/100 ml. or lower.

Table 2 summarizes the serum concentration of sodium, potassium, calcium, phosphorus, chloride, carbon dioxide, and blood glucose, and the hematocrit value on the first day of life in infants born to diabetic mothers. The sodium concentration varied between 130-140 mEq.; potassium 5.2-7.6 mEq.; calcium 2.8-5.1 mEq.; phosphorus 2.65-4.6 mEq.; chlorides 99-107 mEq.; carbon dioxide 17-23.5 mEq.; blood glucose 13-160 mg/100 ml., and hematocrit 49%-71%.

Table 3 summarizes the serum calcium and phosphorus levels in infants on the first day of life born to mothers in prediabetic state. The type of delivery, criteria of the prediabetic state, and the symptoms that the infants exhibited are also presented. Of the 36 infants, 7 were hypocalcemic on the first day of life (19.4%). Four of the

TABLE 2.—*Blood Concentrations of Sodium, Potassium, Calcium, Phosphorus, Chloride, Carbon Dioxide, and Glucose, and Hematocrit Values in Infants of Diabetic Mothers on the First Day of Life*

Patient No.	Na mEq/L.	K mEq/L.	Ca mEq/L.	P mEq/L.	Cl mEq/L.	CO_2 mEq/L.	Blood Glucose Mg/100 Ml.	Hematocrit, %
1	140	—	5.1	3.0	107	—	45	—
2	—	—	5.0	3.84	—	—	48	—
3	—	—	5.0	—	—	—	128	—
4	136	5.5	4.8	2.65	—	—	60	—
5	139	—	4.6	3.67	—	—	86	71
6	130	5.8	4.5	3.46	—	—	109	—
7	134	5.4	4.4	3.3	—	—	63	—
8	132	—	4.3	3.56	—	—	88	61
9	—	5.2	4.3	4.3	—	—	80	—
10	—	—	4.2	4.0	—	21.5	55	—
11	—	5.5	4.2	3.0	—	—	38	—
12	—	—	4.1	4.1	—	—	13	—
13	138	5.7	4.1	3.0	—	—	81	61
14	136	5.3	4.0	3.46	—	—	53	—
15	—	—	4.0	—	—	23.5	—	—
16	138	—	4.0	3.3	—	—	65	—
17	137	5.7	3.5	3.0	—	—	88	49
18	126	6.2	3.5	4.6	—	—	85	—
19	138	7.6	3.05	3.3	—	—	46	—
20	130	—	3.1	4.6	90	19	55	—
21	—	—	3.0	3.13	—	—	116	—
22	140	—	2.8	3.95	105	17	160	57

hypocalcemic infants had edema, pallor, and respiratory distress. Five of the infants who had edema and respiratory distress of short duration had normal serum calcium levels. One infant who exhibited hemorrhagic disease of the newborn with cyanosis, respiratory distress, and convulsions had a calcium level of 8.4 mg/100 ml.

Table 4 summarizes the serum concentrations of sodium, potassium, calcium, phosphorus, chloride, carbon dioxide, blood glucose, and the hematocrit on the first day of life in 36 infants born to mothers in the prediabetic state. The sodium values varied between 128-144 mEq.; potassium 4.3-6.0 mEq.; calcium 3.4-5.1 mEq.; phosphorus 2.3-4.8 mEq.; chloride 100-111 mEq.; carbon dioxide 18-22.6 mEq.; blood glucose 37-197 mg/100 ml.; hematocrit 44%-65%.

One infant in the diabetic series died at the age of 36 hours. The infant's mother had recurrent attacks of ketosis and uncontrolled diabetes. There was one death in the prediabetic group. This was the infant who had hemorrhagic disease of the newborn.

Comment

Hypocalcemia in the neonatal period occurs either on the first day of life [1,10,11] or between the third and fifth days of life.[12-14] The latter type occurs almost exclusively in artificially fed infants. A high phosphorus content of the milk probably plays an important role in the causation of lowered serum calcium in these infants. The etiology of the former type is still unknown. Prematurity, the mode of delivery, and the state of health of the mother appear to be factors in causing the disturbance in calcium metabolism.

In previous studies [1] we noted that hypocalcemia on the first day of life is frequently associated with diabetes mellitus in the mothers, especially in those whose diabetic state was not well controlled. This observation has recently been confirmed by Zetterström and Arnold [15] and Craig.[16] Zetterström et al. measured the serum calcium on the first day of life in 13 out of the 19 infants they studied, and found that the serum calcium concentrations ranged between 6.6-10.7 mg/100 ml. The authors, however, do not state the number of hypo-

TABLE 3.—*Type of Delivery and Criteria of the Prediabetic State in the Mothers: Symptoms, Calcium and Phosphorus in Their Respective Infants*

Patient No.	Type of Delivery	Criteria of the Prediabetic State in the Mothers	Ca (Mg/100 Ml.) in the Infant at Birth	P (Mg/100 Ml.) in the Infant at Birth	Symptoms Observed in the Infant and Outcome
1	Spontaneous delivery	Glucose tolerance curve diabetic-like	10.2	5.5	Edema; recovered
2	Cesarean section	Glucose tolerance curve diabetic-like; diabetes in the family	10.2	4.3	No untoward symptoms
3	Cesarean section	Glucose tolerance curve diabetic-like; glycosuria	10.0	7.2	No untoward symptoms
4	Cesarean section	Glucose tolerance curves diabetic-like with last 3 pregnancies	9.6	7.9	Edema, moon face; respiratory distress of short duration; recovered
5	Spontaneous delivery	Glucose tolerance curve diabetic-like	9.5	5.9	Had a great deal of mucus; recovered
6	Spontaneous delivery	Glucose tolerance curve diabetic-like	9.5	5.2	No untoward symptoms
7	Cesarean section	Glucose tolerance curve diabetic-like	9.4	6.4	No untoward symptoms
8	Cesarean section	Glucose tolerance curve diabetic-like	9.2	6.2	No untoward symptoms
9	Spontaneous delivery	Glucose tolerance curve diabetic-like; diabetes in the family	9.1	6.0	No untoward symptoms
10	Cesarean section	Glucose tolerance curve diabetic-like in several pregnancies	9.1	5.8	No untoward symptoms
11	Cesarean section	Glucose tolerance curve diabetic-like	8.9	4.2	No untoward symptoms
12	Spontaneous delivery	Glycosuria with two previous pregnancies; glucose tolerance curve diabetic-like	8.9	6.7	Edema; shallow, abnormal respirations; cyanosis; recovered
13	Cesarean section	Glucose tolerance curve diabetic-like	8.9	7.8	No untoward symptoms
14	Cesarean section	Glucose tolerance curve diabetic-like; diabetes in the family	8.8	4.8	No untoward symptoms
15	Spontaneous delivery	Glucose tolerance curve diabetic-like	8.8	5.7	No untoward symptoms
16	Spontaneous delivery	Glucose tolerance curve diabetic-like	8.6	4.7	No untoward symptoms
17	Cesarean section	Glucose tolerance curve diabetic-like	8.6	—	No untoward symptoms
18	Cesarean section	Glucose tolerance curve diabetic-like; pre-eclampsia; diabetes in the family	8.6	4.7	No untoward symptoms
19	Spontaneous delivery	Glucose tolerance curve diabetic-like	8.5	7.9	No untoward symptoms
20	Cesarean section	Glucose tolerance curve diabetic-like; diabetes in the family	8.5	6.8	Edema; recovered
21	Spontaneous delivery	Glucose tolerance curve diabetic-like	8.4	7.4	Cyanosis, labored breathing, apnea, convulsions, hemorrhagic diathesis; died
22	Cesarean section	Glucose tolerance curve diabetic-like	8.3	6.3	No untoward symptoms
23	Spontaneous delivery	Glucose tolerance curve diabetic-like; diabetes in the family; obesity	8.3	8.0	Edema; recovered
24	Cesarean section	Glucose tolerance curve diabetic-like	8.3	5.1	No untoward symptoms
25	Cesarean section	Glucose tolerance curve diabetic-like during present and 2 previous pregnancies	8.2	5.4	Mild signs of post-maturity; recovered
26	Cesarean section	Glucose tolerance curve diabetic-like; diabetes in the family	8.2	7.6	No untoward symptoms
27	Spontaneous delivery	Glucose tolerance curve diabetic-like	8.1	5.8	No untoward symptoms
28	Medical induction	Glucose tolerance curve diabetic-like	8.0	5.7	No untoward symptoms
29	Cesarean section	Glucose tolerance curve diabetic-like	8.0	8.4	No untoward symptoms
30	Cesarean section	Glucose tolerance curve diabetic-like	7.6	6.8	No untoward symptoms
31	Cesarean section	Glucose tolerance curve diabetic-like; diabetes in the family	7.6	6.0	Pallor, moderate grunt 1st. day; recovered
32	Cesarean section	Glucose tolerance curve diabetic-like; diabetes in the family	7.4	6.2	Mild respiratory distress 1st. day; recovered
33	Cesarean section	Glucose tolerance curve diabetic-like, with 3 pregnancies; diabetes in the family	7.4	6.6	Edema, shallow respirations; recovered
34	Cesarean section	Glucose tolerance curve diabetic-like	7.1	9.0	Edema; recovered
35	Cesarean section	Glucose tolerance curve diabetic-like; diabetes in the family	6.8	4.9	No untoward symptoms
36	Spontaneous delivery	Glucose tolerance curve diabetic-like	6.8	6.4	Rapid respiration; slight chest retraction; recovered

TABLE 4.—*Blood Concentrations of Sodium, Potassium, Calcium, Phophorus, Chloride, Carbon Dioxide, and Glucose, and Hematocrit Values in Infants of Prediabetic Mothers on the First Day of Life*

Patient No.	Na mEq/L.	K mEq/L.	Ca mEq/L.	P mEq/L.	Cl mEq/L.	CO_2 mEq/L.	Blood Glucose Mg/100 Ml.	Hematocrit, %
1	—	—	5.1	3.0	—	—	63	—
2	137	—	5.1	2.3	—	—	41	—
3	137	—	5.0	3.9	111	—	45	—
4	—	—	4.8	4.3	—	—	—	—
5	138	—	4.75	3.2	—	—	70	—
6	—	—	4.75	2.8	—	—	37	—
7	—	—	4.7	3.46	—	—	—	—
8	135	—	4.6	3.0	105	—	60	—
9	136	—	4.55	3.24	105	—	50	—
10	129	—	4.55	3.1	—	—	63	—
11	136	4.8	4.45	2.3	107	—	60	—
12	—	—	4.45	3.62	—	—	—	—
13	—	—	4.4	4.2	—	—	—	—
14	134	—	4.4	2.6	—	—	45	—
15	144	—	4.4	3.0	108	—	61	—
16	136	—	4.3	2.54	—	—	—	—
17	133	4.5	4.3	—	102	24	—	61
18	128	4.8	4.3	2.54	—	—	87	55
19	—	5.0	4.25	4.27	—	—	58	—
20	142	6.0	4.25	3.67	—	—	83	—
21	135	5.75	4.2	3.83	102	20	—	60
22	143	4.3	4.15	3.4	—	—	61	—
23	144	—	4.15	4.3	107	—	85	—
24	134	—	4.1	2.75	101	18	60	65
25	—	—	4.1	3.0	—	—	—	—
26	—	—	4.1	4.1	—	—	—	—
27	139	5.0	4.05	3.1	—	—	40	—
28	134	5.6	4.0	3.0	—	—	109	44
29	142	—	4.0	4.5	—	—	—	—
30	138	—	3.8	3.67	100	19.8	42	—
31	137	5.2	3.8	3.24	—	—	197	50
32	131	5.8	3.7	3.34	—	22.6	72	59
33	130	—	3.7	3.56	—	—	85	—
34	137	—	3.55	4.8	103	—	65	—
35	—	—	3.4	2.64	—	—	—	—
36	135	—	3.4	3.46	100	—	45	—

calcemias they observed. Craig [16] reported that hypocalcemia occurred in 9 out of 14 infants born to diabetic mothers and in 1 out of the 2 infants born to mothers in the prediabetic state. Only in three infants, however, was the calcium measured on the first day of life. The state of control of the diabetes in the respective mothers is not described. We noted a statistically significant lower mean serum calcium level in the infants born to diabetic and prediabetic mothers when compared with the mean serum calcium of infants of normal mothers (Table 6). The over-all incidence of hypocalcemia in infants of diabetic mothers was 27.3%, and it was 19.4% in infants of prediabetic mothers. In the 19 infants whose mothers' diabetic state was adequately controlled there were 3 instances of hypocalcemia—an incidence of only 16.0%. The three mothers whose diabetes was poorly controlled gave birth to infants all of whom had hypocalcemia. With the exception of two, all infants in the diabetic series were born by cesarean section. In 17 of these, born to mother whose diabetes was adequately controlled, there were 2 infants with hypocalcemia, an incidence of 11.8%. This figure compares favorably with an incidence of 13.7% reported previously in infants delivered by section because of cephalopelvic disproportion or because of repeat section.[1] The effect of cesarean section on calcium metabolism in infants of diabetic mothers was also observed by Zetterström et al.[15]

In the prediabetic series 23 infants were delivered by cesarean section. Six of these

TABLE 5.—*A Comparison of Incidence of Hypocalcemia in Infants Born by Cesarean Section to (1) Mothers with Cephalopelvic Disproportion or Repeat Section, (2) Abnormal Pregnancies and/or Labor, (3) Diabetes Mellitus-Controlled, (4) Mothers in Prediabetic State*

Indications for Cesarean Section	No. of Infants	Hypocalcemia	%
C. P. disproportion or repeat section	51	7	13.7
Abnormal pregnancy and/or labor	19	7	36.8
Diabetes mellitus controlled	17	2	11.8
Prediabetic state	23	6	26

had hypocalcemia, an incidence of 26% (Table 5). Since infants born by cesarean section to mothers who had abnormal pregnancies had an incidence of hypocalcemia of 36.7%,[1] an incidence of hypocalcemia of 26% in infants of prediabetic mothers would tend to substantiate the hypothesis that these mothers, though they are not full-blown diabetics, are probably suffering from some metabolic derangement, the nature of which is not yet defined.

In a previous publication [1] we noted that the mean serum phosphorus concentration on the first day of life in 824 infants was 5.7± S. D. 0.7. A serum phosphorus above 7.1 mg/100 ml. would be considered hyperphosphatemia. Using this criteria we found that 6 out of the 22 infants born to diabetic mothers and 8 out of 36 infants born to mothers in the prediabetic state had hyperphosphatemia. Comparing the mean phosphorus concentration of the two groups of infants with the mean phosphorus concentration of normal newborns on the first day of life, we find a significantly higher mean serum phosphorus in the two groups studied (Table 6). There is no statistically significant difference between the mean phosphorus values of the two groups. Zetterström et al. found hyperphosphatemic levels varying from 9.1-14.9 mg/100 ml. in all of the 10 infants they studied on the first day of life. We found hyperphosphatemia in each of the three infants born to diabetic mothers whose diabetes was poorly controlled. It appears that uncontrollable diabetes may be a factor in the causation of hyperphosphatemia. Zetterström et al. do not mention the degree of control of the diabetic mothers whose infants they observed.

Lowrey et al.[18] in their study of 11 infants of diabetic mothers found severe uncompensated acidosis and variable total base and chloride concentrations in most of the infants. Out of 11 infants, 4 showed a reduction in the concentration of base (143-144 mEq.). In none of the hypocalcemic infants who had symptoms of respiratory distress, edema, or convulsions did we find abnormal levels of sodium. The potassium levels were normal in all infants in the diabetic group with the exception of two whose potassium levels were "high." These two also had hypocalcemia. One infant in the prediabetic series had a potassium concentration of 6.0 mEq. In most instances a high potassium level was associated with a lowered calcium concentration. The chloride values were all in the normal range. The carbon dioxide values were generally within the normal range. There was no statistically significant difference between the mean glucose levels on the first

TABLE 6.—*A Comparison of Mean Concentrations of Calcium and Phosphorus in Infants on the First Day of Life Born to Normal, Diabetic, and Prediabetic Mothers*

		Calcium Mg/100 Ml.			Inorganic Phorphorus Mg/100 Ml.		
Mothers	Infants, No.	Mean±S. D.	Range	"P"	Mean±S. D.	Range	"P"
Normal	824	9.2±0.6	7.3-12	<0.01	5.7±0.7	4.0-7.4	<0.01
Diabetic	22	8.2±1.3	5.6-10.2		6.6±1.0	4.9-8.5	
Normal	824	9.2±0.6	7.3-12	<0.01	5.7±0.7	4.0-7.4	<0.01
Prediabetic	36	8.5±0.9	6.8-10.2		6.3±1.2	4.2-9.0	
Diabetic	22	8.2±1.3	5.6-10.2	>0.2	6.6±1.0	4.9-8.5	>0.1
Prediabetic	36	8.5±0.9	6.8-10.2		6.3±1.2	4.2-9.0	

TABLE 7.—*A Comparison of Mean Glucose Levels of Infants on the First Day of Life Born to Normal, Diabetic, and Prediabetic Mothers*

Mothers	Infants, No.	Mean Glucose Level	S. D.	"p"
Normal	66	55	±17.9	<0.01
Diabetic	20	69	±27.8	
Normal	66	55	±17.9	>0.1
Prediabetic	24	62	±17.5	
Diabetic	20	69	±27.8	>0.3
Prediabetic	24	62	±17.5	

day of life in the infants born to diabetic mothers and those born to mothers in the prediabetic state ($P>0.3$), but the mean glucose level in the diabetic series is significantly higher than the mean glucose level of normal infants on the first day of life ($P<0.01$) (Table 7).[17]

Conclusions

1. There is an increased incidence of hypocalcemia on the first day of life in the infants born to mothers who are diabetic or in the prediabetic state.

2. In the infants whose mothers' diabetes is adequately controlled the incidence of hypocalcemia appears to be related to the mode of delivery (cesarean section).

3. In each of three instances where the control of diabetes of the mother was poor, the infant had hypocalcemia on the first day of life.

4. The incidence of hypocalcemia is highest in the offspring of mothers who are in the prediabetic state, indicating that a metabolic disturbance probably played an etiologic role in the causation of the hypocalcemia.

5. The mean serum phosphorus in both the diabetic and the prediabetic series was higher than the mean phosphorus found in normal infants on the first day of life. However, hyperphosphatemic levels occurred in only 6 of the 22 infants born to the diabetic mothers and in 8 out of 36 born to the mothers in the prediabetic state.

6. The sodium, total carbon dioxide, and chloride levels in the serum showed no marked deviations from normal in either group.

7. The potassium levels in the diabetic series tended to be higher than normal. This was particularly true in infants who had hypocalcemia.

8. The mean glucose level on the first day of life was significantly higher in the diabetic group when compared with the mean glucose level of normal infants on the first day of life. There was no statistically significant difference between the mean glucose levels of the two groups.

555 Prospect Place.

REFERENCES

1. Gittleman, I. F.; Pincus, J. B.; Schmerzler, E., and Saito, M.: Hypocalcemia Occurring on the First Day of Life in Mature and Premature Infants, Pediatrics 18:721, 1956.

2. Sobel, A. E., and Sobel, B. A.: Microestimation of Calcium in Serum, J. Biol. Chem. 129:721, 1939.

3. Sobel, A. E.: Microestimation of Inorganic Phosphate, Indust. & Engin. Chem. (Analyt. Ed.) 17:242, 1945.

4. Natelson, S.: Routine Use of Ultramicro Methods in the Clinical Laboratory, Am. J. Clin. Path. 21:1153, 1951.

5. Natelson, S.: Routine of the Perkin-Elmer Flame Photometer in the Clinical Laboratory, Am. J. Clin. Path. 20:463, 1950.

6. Kopp-Natelson Micro-Gasometer, Model 511, Kopp Scientific Instruments, Inc., 15 Park St., Springfield 5, Mass.

7. Sobel, A. E., and Hanok, A.: Ultramicro Quantitative Analysis in Clinical Laboratories, Microchemie 39:51, 1952.

8. Schales, O., and Schales, S. S.: Simple and Accurate Method for Determination of Chloride in Biological Fluids, J. Biol. Chem. 140:879, 1941.

9. Sobel, A. E., and Kraus, G.: Micro Modification of Folin-Wu, presented at the International Pediatric Congress, 1947.

10. Willi, H.: Die Neugeborenenspasmophilie, Monatschr. Kinderh. 80:309, 1939.

11. Dodd, K., and Rapoport, S.: Hypocalcemia in the Neonatal Period, Am. J. Dis. Child. 78:537, 1949.

12. Bakwin, H.: Pathogenesis of Tetany of the New-Born, Am. J. Dis. Child. 54:1211, 1937.

13. Gardner, L. I.; MacLachlan, E. H.; Pick, W.; Terry, M. L., and Butler, A. M.: Etiologic Factors in Tetany of Newly Born Infants, Pediatrics 5:228, 1950.

14. Gittleman, I. F., and Pincus, J. B.: Influence of Diet on the Occurrence of Hyperphosphatemia and Hypocalcemia in the Newborn Infant, Pediatrics 8:778, 1951.

15. Zetterström, R., and Arnold, R. G.: Impaired Calcium-Phosphate Homeostasis in Newborn Infants of Diabetic Mothers, Acta paediat. 47:107, 112, 1958.

16. Craig, W. S.: Clinical Signs of Neonatal Tetany, with Especial Reference to Their Occurrence in Newborn Babies of Diabetic Mothers, Pediatrics 22:297, 1958.

17. Gittleman, I. F., and Pincus, J. B.: Blood Sugar and Citric Acid Levels in Newborn Infants, Pediatrics 9:38, 1952.

18. Lowrey, G. H.; Graham, B. D., and Tsao, M. U.: Chemical Homeostasis in the Newborn Infants of Diabetic Mothers, Pediatrics 13:527, 1954.

Incidence of Viral Parotitis in the Domestic Dog

FRANK NOICE, Ph.D.; F. M. BOLIN, D.V.M., and D. F. EVELETH, Ph.D., D.V.M., Fargo, N. D.

Within recent months we have had an opportunity to observe two separate cases of dogs having severe parotitis. In each case the glands were swollen and tender to pressure. From both animals a virus was isolated from the saliva. In one case a sequence of serum specimens were positive for mumps virus by complement-fixation tests.

The susceptibility of monkeys for the mumps virus upon direct parotid gland inoculation or cannulation of Stensen's duct is well documented.[1,2] However, the occurrence of mumps virus in other animals is not definite or not considered too probable. Wollstein[3] conducted experiments in 1916 in the transmission of mumps from humans to the domestic cat. Her findings showed that the cat, upon direct inoculation into the parotid gland and/or testis of either saliva or defibrinated blood from human mumps cases, displayed clinical symptoms typical of infectious mumps. She found that only young cats were susceptible in transmission trials. Wollstein[4] repeated her experiment in 1918 with similar positive findings. Seiffert[5] reports that others had attempted to confirm Wollstein's findings without success. Upon a review of literature it was concluded that little has been reported in the transmission of mumps to species other than man and monkeys.

Submitted for publication Dec. 8, 1958.

Report on Project No. S-16-2M.

Published with the approval of the Director, North Dakota Agricultural Experiment Station.

The authors acknowledge the assistance of A. A. Gustafson, Director of the State Public Health Laboratory, Grand Forks, N. D.

Department of Veterinary Science, North Dakota Agricultural College. Dr. Noice is also on the staff at Concordia College, Moorhead, Minn.

Report of Cases

CASE 8-321A.—A 6-month-old dachshund, the pet of family in which three juvenile members were under medical care for mumps. The dog was allowed upon the beds of the patients during their illness and convalescence. While the three patients were still recovering from their illness the dog became sick, refused food, became recumbent, and developed swollen parotid glands. It was at this time that the animal was brought to our laboratory, where saliva and blood specimens were collected. Before a second examination, scheduled 10 days later, the animal died, and the cadaver was not submitted for postmortem studies.

CASE 8-450A.—A 3-month-old Boston terrier, brought to our attention six weeks after Case 8-321A. This case displayed extremely enlarged parotid glands, more pronounced than the previous case. While the history of this dog indicated a normal appetite, it had considerable difficulty in chewing and demonstrated pain upon swallowing. The family in which Case 8-450A was a pet had three children all under medical treatment for mumps. The first child to have mumps was just recovering from the disease when the second child was diagnosed as positive for mumps. The Boston terrier and the third child both became ill five days after the second child had been diagnosed. Again the dog had been allowed upon the beds of the ill children and was in the sickrooms considerably during the daytime hours. Saliva and a blood specimen were collected, and the dog was returned to our laboratory 14 days later, at which time a second blood specimen was obtained. At the time of the second examination the Boston terrier displayed no swelling or sensitiveness of the parotid glands and appeared to be normal in health.

Experimental Studies

Methods and Materials

The saliva from both cases was processed for primary embryonated hen egg passage by modifying the methods of Enders.[6] The saliva specimens were diluted with about one-third their volumes with infusion broth and centrifuged for five minutes at 2,500 rpm. The supernatant fluid was decanted and centrifuged a second time. Penicillin, 1,000 units and streptomycin, 1,000μg. per milli-

liter, were added to the finally decanted supernatant fluids, which were stored in the refrigerator for one hour prior to inoculation. Blood specimens from Case 8-450A were centrifuged for serum separation and stored in the refrigerator for serological studies.

Primary Virus Isolation in Chick Embryos

Five 6-day-old eggs were injected with 0.1 ml. of the prepared saliva inoculum from Case 8-321A via the yolk sac route and incubated at 37 C. After six days' incubation two embryos were dead, and a third was dead after a total of eight days' incubation. The three remaining embryos of the trial survived. Allantoic fluid harvested from one of the viral destroyed eggs was cultured for bacterial contamination and stored in the refrigerator over night until the cultures for sterility were examined and found negative. A second series of five 6-day-old eggs were each injected with 0.1 ml. of the previously harvested allantoic fluid. Of the second passage two of the five embryos were destroyed after seven days' incubation. The remaining three eggs of the second passage survived. At the time these egg studies were being conducted the animal (Case 8-321A) died and the virus studies were terminated after the second egg passage.

The saliva of Case 8-450A was prepared and injected into six 6-day-old eggs. Three of the six eggs in the primary passage died within seven days' incubation. The remaining three test eggs survived. Allantoic fluids of the positive eggs were harvested, pooled, and found bacteria-free. Each harvest of allantoic fluid was individually found positive for hemagglutins with 10% chicken red cells by the slide technique prior to pooling. The second egg passage into six 6-day-old eggs again resulted in three of the six eggs being destroyed. The maximum incubation time required in the second passage was nine days. The allantoic fluid of the positive eggs was processed as before and stored at −20 C.

Virus Propagation in Tissue Culture

HeLa cells which were obtained from the Microbiological Associates, Inc., 4846 Bethesda Avenue, Washington, D. C., were grown in 15×125 mm. screw cap test tubes in a medium of 90% medium 199 and 10% horse serum. The tubes were contained in a stationary rack at a 5-degree angle and incubated at 37 C for four days, at which time a flourishing monolayer was established. Such tubes were well maintained for 8-10 days without subsequent feeding.

The methods of propagation of the allantoic strain of virus in tissue culture were according to Henle and Deinhardt.[7] Allantoic fluids in the amounts of 0.1 ml. were inoculated into an experimental series of tubes of HeLa cells. Virus cytolitic and degenerative lesions were noted within 48 hours and such lesions remained quite stationary. The virus fluid from such tubes was harvested after eight days' incubation and used as an inoculum for a second passage. The degenerative lesions were produced within 48 hours consistently through six passages of HeLa cells. In subsequent passages the degenerative lesions required a progressively greater length of time to become established, and by the 15th passage lesions were not noted before seven days of incubation. In the 19th passage no degenerative lesions were observed. A second trial with the same originally isolated strain of allantoic virus gave similar results in the HeLa cell passages. In Trial 2, consistent degenerative lesions occurred within 48 hours for five passages, progressively greater time being required for lesion production, until no lesions were noted in the 16th passage.

Serology

The two blood specimens obtained 14 days apart from Case 8-450A were subjected to the mumps complement-fixation test using diagnostic mumps viral antigen obtained from Lederle Laboratories. The method of conducting the test was according to Kolmer et al.[8] The first serum specimen collected at an early acute stage of infection was negative for mumps antibodies. However, the second serum specimen obtained 14 days later, and upon apparent recovery from ill-

ness, was positive to the mumps complement-fixation test at dilutions of 1:32.

Tube technique hemagglutination inhibition studies according to Enders[6] were conducted with virus-containing allantonic fluid, which was previously found positive for hemagglutinins by the slide technique, and standard mumps-immune guinea pig serum obtained from Lederle Laboratories. Such mump antiserum effectively inhibited the agglutination properties of the dog strain of virus.

Summary

Two dogs examined were found to have severe parotitis, one of the dogs, No. 8-450A, being positive for mumps virus by the complement-fixation test. In both cases processed saliva specimens revealed a virus capable of killing embryonated hens' eggs and was inhibited for its hemagglutination properties by a standard human mumps antiserum. From one case a cytolytic virus was isolated, with use of HeLa cell tissue cultures. The virulence in vitro appeared to decrease with progressive subpassages to a point of no cytolytic activity.

State College Station.

REFERENCES

1. Rhodes, A. J., and Van Rooyen, C. E.: Textbook of Virology for Students and Practitioners of Medicine, Ed. 3, Baltimore, The Williams & Wilkins Company, 1958.

2. Rivers, T. M., Editor: Viral and Rickettsial Infections of Man, Ed. 3, Philadelphia, J. B. Lippincott Co., 1959.

3. Wollstein, M. J.: J. Exper. Med. 23:353, 1916.

4. Wollstein, M. J.: J. Exper. Med. 28:377, 1918.

5. Seiffert, G.: Virus Diseases in Man, Animal and Plant, New York, Philosophical Library, 1944.

6. Enders, J. F., in Diagnostic Procedures for Virus and Rickettsial Diseases, American Public Health Association, New York, 1948, p. 139.

7. Henle, G., and Deinhardt, F.: Proc. Exper. Biol. & Med. 89:556, 1955.

8. Kolmer, J. A.; Spaulding, E. H., and Robinson, H. W.: Approved Laboratory Technic, Ed. 5, New York, Appleton-Century-Crofts, Inc., 1951.

Hereditary Hematuria

EDWIN P. RUSSELL, M.D., Los Angeles, and NATHAN J. SMITH, M.D., Madison, Wis.

Idiopathic hematuria as a familial, genetically controlled disease is unusual. Reyersbach et al.[1] identified this condition in only eight patients in an 18-year period in a large pediatric clinic. Hematuria, per se, is a commonly encountered clinical finding, and that this finding can result from some undefined genetically controlled abnormality must be frequently considered if rather disastrous diagnostic errors are to be avoided.

Three persons with asymptomatic hematuria and one who was asymptomatic for about 15 years and eventually succumbed to nephritis have been found in the family to be discussed here. An attempt has been made to gain some insight into the nature of the genetic transmission of the abnormality. The natural history of the disturbance is of interest with particular regard to the long-term prognosis in children found to have this condition.

Family History

The propositus, Case 1, was seen by one of us (E. P. R.) when 8 years of age. He was said to be suffering from chronic glomerulonephritis of over two years' duration with rather persistent gross hematuria. The absence of other evidence of disease after so long a period with grossly manifest abnormal urine suggested that the diagnosis should be reevaluated.

The family history revealed that the only sibling of the propositus, an 11-year-old girl, also had been found to have hematuria. The hematuria had disappeared for a period but was subsequently found to be present during the present study. The mother of the propositus has never been known to have had hematuria. She has had frequent medical examinations in recent years with microscopic study of the urine. Two maternal uncles of the propositus have been known to have had asymptomatic hematuria for many years. Both have married and have a total of three children, none of whom have abnormal urine. There is one additional maternal uncle whose urine is not abnormal. There are no maternal aunts.

The maternal grandmother of the propositus is living and well. She is one of nine children with four siblings who are living and well. There is no history of hematuria or findings in their histories suggestive of renal disease in the four siblings who are not living. The parents of the maternal grandmother were of Scotch, English, and French ancestry. They are not living, but there was nothing in their history suggestive of renal disease. The maternal grandfather of the propositus died of a "stroke." He was one of five children, and his four siblings are living and well. His father died of uremia. His mother is still living and well, and there is no instance of renal disease in her history. A review of these persons' medical histories revealed no visual or auditory symptoms, and, except for the father of the maternal grandfather of the propositus, no history of hematuria. The son of a brother of the maternal grandmother of the propositus died of "nephritis" at the age of 44 years, and a daughter age 45 is now living and is reported to have "nephritis."

The father of the propositus is of Jewish extraction. He had a residual paresis of the left lower extremity which followed an

Submitted for publication Jan. 19, 1959.

Assistant Clinical Professor of Pediatrics, University of California Medical Center at Los Angeles (Dr. Russell). Alfred Dorance Daniels Professor of Pediatrics and Chairman, Department of Pediatrics, University of Wisconsin School of Medicine (Dr. Smith).

attack of poliomyelitis in early life. He has mild hypertension and coronary heart disease. Recently several small urinary calculi were passed spontaneously with resultant transient hematuria which rapidly cleared. There had never been urine abnormalities previous to this episode. The family history of the father of the propositus was reviewed in detail, and no instances of urinary abnormality, or visual or auditory disturbances were present.

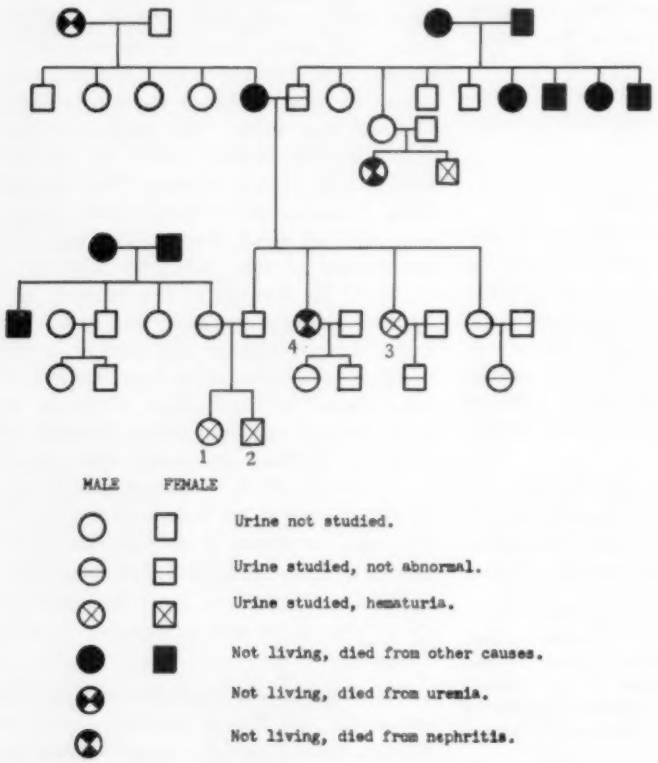
These findings would indicate that the asymptomatic hematuria found in the propositus was a familial abnormality transmitted from his maternal ancestry. The genetic transmission is most likely in keeping with a dominant mode of transmission (Figure).

Report of Cases

CASE 1.—Birth date Dec. 26, 1946. This boy was born after a normal pregnancy and enjoyed good health until he was 3 years old. At that time symptoms of pallor, weight loss, and constipation, all of mild degree, were noted. Symptomatic treatment directed principally at relieving the constipation was successful in alleviating the symptoms. No urine studies were made at this time. Occasional mild and moderately severe infections of the upper respiratory tract occurred during his fourth, fifth, and sixth years.

He was first seen by us (E. P. R.) at 6 years of age (April 1, 1952) with mild gastroenteritis and fever. He made a prompt recovery without medication. The urine was not examined at this time. Shortly after this episode he left this community and was not seen again by us until he was 8 years old (Oct. 14, 1954), when the family returned here.

In the interim, his urine had been examined as part of a school health examination (June 4, 1952), and marked hematuria was found. His sister was also found to have hematuria at this time. Several physicians were consulted, and a diagnosis of chronic glomerulonephritis was made. Six weeks of bed rest failed to change the urinary findings, and he was gradually returned to normal activity.



Ancestry chart of propositus.

The tonsils were removed in 1953. The parents had been extensively cautioned about the dangers of recurrent respiratory infections in patients with nephritis and became disturbingly overprotective and solicitous in the management of the child.

When seen in October, 1954, he had a mild upper respiratory tract infection but was found to be well nourished, alert, and cooperative. On physical examination, the only remarkable finding concerned the left testis, which was high in the inguinal canal. The blood pressure was 95/65 mm. Hg. The urine contained large numbers of erythrocytes, some leukocytes, but casts were not seen. Albuminuria was not present. The mother stated that in the past two years the urine had never been completely free of blood, and the degree of hematuria was severer when infections were present. To her knowledge his blood pressure had never been elevated, and, although several blood chemistry studies had been done, there had never been any evidence of nitrogen retention.

At this time the family history was reviewed, and it was found that a maternal uncle had suffered from transient thrombocytopenia associated with hematuria. Studies to identify any primary hemostatic defect in the propositus were performed and revealed normal bleeding and clotting times. The platelet count, tourniquet test, and clot retraction were normal. A prothrombin time and prothrombin consumption test were normal. It was of interest that the patient had been circumcised, had had a tonsillectomy and several instances of moderately severe trauma without manifestations of undue hemorrhage.

After these studies the patient was seen by a consulting urologist (W. E. Goodwin, M.D.),[8] and was hospitalized for study. Cystoscopy and retrograde pyelograms, a cystogram, and a urethragram were done. Hematuria was present in specimens from each ureter. No evidence was found of any gross anatomical abnormality in the upper or lower urinary tract.

While the patient was in the hospital the urine was examined repeatedly. Varying degrees of moderately severe hematuria were always present prior to cystoscopy. Position and activity did not influence the degree of hematuria. A rare granular cast could be found in the centrifuged sediment of the urine. The urine was sterile, and the tuberculin skin test was negative. The urea clearance test was normal. The nonprotein nitrogen was 39 mg. % and the blood urea nitrogen level was 10 mg. %. The blood count had remained normal and the blood pressure was repeatedly normal, e. g., 110/70 mm. of mercury.

He was next seen by one of us (E. P. R.) on Aug. 8, 1955. In the interim he had led a normal active existence. Hematuria had continued unrelated in severity to any normal variation in activity. He weighed 85¾ lb. and was 51¾ in. tall. His urine contained large numbers of erythrocytes. His blood count and hemoglobin level were normal, and his blood pressure was not elevated. A recently performed audiogram failed to identify any auditory defect.

The family again moved to New York, where the propositus was followed by Conrad Riley, M.D., at the Columbia-Presbyterian Medical Center. In a personal communication dated Sept. 3, 1957, Dr. Riley stated, "Meanwhile . . . status remains essentially the same. We have hopefully tried him on steroids but have seen no change in his urinary findings with this approach."

In a personal communication dated Sept. 25, 1958, Peter R. Scaglione, M.D., wrote:

"On Nov. 17, 1956, the boy was treated with prednisone 15 mg. q. 6 h. orally in order to observe the effect of steroids on the course of his chronic renal process. Prior to the start of the therapy, base-line studies done in the fasting state revealed E. S. R. (Westergren) 23 mm/1 hr.; NPN 30 mg. %; zinc turbidity 6.6 units (Kunkel), and serum protein partition by paper electrophoresis as tabulated below:

	Normal	Patient
albumin gm. %	3.3	3.2
α_1-globulin	0.2	0.5
α_2-globulin	0.7	1.1
β-globulin	1.2	1.1
γ-globulin	1.8	1.3
Tot. Prot. gm. %	7.4	7.3

"On the third day of therapy the NPN was 27 mg.; E. S. R. 15 mm.; B. P. 135/80; urinalysis: protein 3 plus and many RBC/H. P. F. Body weight was stable at 112 lb. The boy complained of occasional headaches, an event which caused profound anxiety in the mother. Consequently therapy was discontinued on about the tenth day. The day before stopping treatment, a urinalysis revealed protein 1 plus and 50 RBC/H. P. F.

"It seems clear that the steroid as used above had no effect on the urinary findings."

He was last seen by one of us (E. P. R.) on Aug. 6, 1958. His height was 57½ in. and he weighed 108½ lb. He was in excellent health, tending to be somewhat obese. His mother stated that he had reduced his weight by 8 lb. during the summer. His hearing and vision were still excellent. There was nothing noteworthy in his physical examination except an allergic conjunctivitis, which has troubled him for a number of years. His blood pressure was 120 systolic and 70 diastolic. The hemoglobin was 10.7 gm. The urine was reported as follows: Sp. gr. 1.019, albumin 4 +, sugar 0, WBC many, RBC loaded, and an occasional granular cast.

Case 2.—Sister of the propositus, birth date Sept. 21, 1943. This girl was born after a normal

pregnancy and uneventful labor. Her health has been good with the exception of the following illnesses from which she has recovered without sequelae.

A persistent mild atopic dermatitis began at 5 years of age. Some hearing loss was noted at 7 years of age but was corrected after a tonsillectomy and adenoidectomy. She had epidemic parotitis in 1951, varicella in 1952, and rubeola in 1953. She has had frequent upper respiratory tract infections.

In April, 1952, a urinalysis performed as part of a school health examination revealed microscopic hematuria (4 erythrocytes per high power field). This finding persisted for several weeks in spite of a period of six weeks of bed rest. During this time her blood urea nitrogen level was normal (11.7 mg. %) and an intravenous pyelogram revealed no abnormalities. The blood pressure, weight gain, and physical examination were reported as normal.

It was first possible to study this patient in March, 1955. At that time she was suffering from acute appendicitis and underwent an appendectomy without complication. The urine was found to contain over 100 erythrocytes per high-power field. No casts were seen. The blood urea nitrogen was 12.5 mg. %. The nonprotein nitrogen was 31 mg. %. The PSP excretion study was normal, as were the serum proteins and the urea clearance. The blood pressure was taken at four-hour intervals for two days and was always normal.

Varying degrees of microscopic hematuria were consistently found during the hospitalization and persisted after her discharge from the hospital.

The family returned to New York and she was not seen by us again until Aug. 6, 1958. The mother reported that the daughter had been entirely well in the interim except for some rather vague complaints of "lower spinal trouble" for which she had been seen by an orthopedic surgeon. She reported that the hematuria had cleared.

Upon examination the sister of the propositus presented the picture of a very healthy, well-adjusted, adolescent girl. Her height was 60¼ in. and she weighed 104 lb. There was nothing noteworthy in her physical examination. Her hearing and vision were normal. Her blood pressure was 105/74. A tuberculin test was negative. The hemoglobin was 11.4 gm. The urine was found to show pH 8; Sp. Gr. 1.021; albumin, faint trace; sugar 0, WBC occasional, and RBC none.

CASE 3.—Youngest of three maternal uncles of the propositus, birth date 1927. A review of his history revealed that hematuria was first discovered in his urine in 1940. A diagnosis of glomerulonephritis was made. He was treated with bed rest for two months, following which his urine was found to be normal. Upon his resuming normal activity hematuria recurred, and it has been constantly present since that time.

He was inducted into the Army in 1945, and after one month was hospitalized because of hematuria. After six months' observation in a military hospital he was discharged from the Army because "he had blood in his urine for which no cause could be found." Records of this hospitalization are not available.

After his discharge from the Army he became a student. In 1949, he was again hospitalized because of his concern regarding persistent hematuria and mild, dull, low-back pain. A review of the records of this hospitalization revealed that the physical examination was unremarkable. The blood pressure was 120/70 mm. of mercury. The urinalyses showed constant microscopic or gross hematuria. No casts were found. Cultures of the urine were negative. The urea clearance was normal. Intravenous and retrograde pyelography failed to reveal any abnormality. The serum protein level and A/G ratio were normal. The blood count was normal except for platelet counts ranging from 100,000 to 200,000 per cubic millimeter. The tourniquet test was positive, and a diagnosis of idiopathic thrombocytopenic purpura was considered. Rutin, 80 mg. daily, was prescribed but failed to affect the hematuria.

Six months after these observations were made, this patient was reported to have bled for eight days after a tooth extraction. His history showed that he was somewhat anemic when seen during this episode, and a platelet count of 20,000 per cubic millimeter was found. Blood transfusions and local hemostatic therapy controlled the bleeding. The platelet count subsequently returned to normal levels with no notable effect on the degree of hematuria which persisted.

He was studied again in March, 1955. There was gross hematuria, a normal intravenous pyelogram, and normal PSP excretion. Occasional granular casts were found for the first time in the urine at the time of this study.

In May, 1955, he was rejected for employment because of hematuria. One of us (E. P. R.) wrote to his prospective employer recommending employment, and he was accepted.

Recently he became eligible for promotion, and his firm sent him to Duke University, where he was hospitalized and studied again. Their findings resulted in a report of hematuria compatible with normal employment, and he was promoted on their recommendation.

CASE 4.—Maternal uncle of the propositus, birth date 1917. A review of his history showed that he enjoyed normal health until 1941, when he was examined for military service. Persistent hematuria was found, and he was not accepted for military duty. He was studied at that time, and a tentative

diagnosis of polycystic disease of the kidneys was made. The findings on intravenous pyelography did not support this diagnosis. Since that time this man has chosen to minimize his abnormality and refused further study or observation regarding this problem.

His family physician reported that he had led a normally active life. He also reported that this patient had had persistent hematuria, some cylindruria, and moderately severe hypertension, the blood pressure being 170/100 mm. of mercury. The degree of hematuria was thought to have varied in proportion to the amount of the patient's physical activity. During his final illness there were occasions when his urine was free from blood.

This maternal uncle of the propositus died on Aug. 18, 1956, at the age of 40. The final diagnosis given by T. E. Stanley, M.D., of St. Elizabeth's Hospital, Richmond, Va. (as a result of his studies during the patient's final hospitalization in June, 1956) were as follows: "1. Acute exacerbation of chronic glomerulonephritis with uremia. 2. Papilledema. 3. Anemia. 4. Hypertensive cardiovascular disease."

Comment

Hematuria must always be considered a serious symptom, and few, if any, of the known causes of blood loss into the urine can be regarded lightly. Glomerulonephritis, neoplasm, and infection of the urinary tract are commonly recognized causes of urinary tract bleeding. In recent years, an ever-growing list of less common causes of hematuria have been identified, and fewer instances of "idiopathic" hematuria remain.

Patients such as the propositus in the family discussed here present challenging problems, and the error made in making a diagnosis of chronic glomerulonephritis had disastrous repercussions in the profound alterations its guarded prognosis caused in intrafamily emotional relationships. The absence of azotemia, hypertension, growth alteration, and disturbed renal function should be strong evidence against the diagnosis of chronic glomerulonephritis. Likewise, the striking family history might alert one to suspect some unusual urinary tract disturbance other than nephritis, although "familial nephritis" has been described.

Of primary interest in the patients discussed here is the unusual family history of hematuria involving four generations. It would appear that the abnormality is transmitted as a dominant trait. In these limited observations, it appears that females are less severely affected than the males, a finding similar to that of Alport [3] in one extensively studied family with hereditary hematuria.

The absence of other congenital abnormalities in this family is of interest, especially as regards nerve deafness. In the family reported by Alport, a high incidence of this defect was found in those members free of hematuria as well as those having abnormal urine. Reyersbach and Butler [1] found nerve deafness in three of eight patients with hereditary hematuria. On historical evidence only, this abnormality has not been present in the family described in this report.

The extremely limited experience recorded in the literature and the limited nature of our observations in this family make it quite impossible to give any definitive statement regarding ultimate prognosis in the affected individuals with hereditary hematuria. Early in life the disease seems to be accompanied by few disabling symptoms. Guthrie [4] studied a family, later reported by Alport,[3] for seven years and felt the course of the disease to be completely benign. When Alport reviewed the same family many years later it was disturbing to find that several of the affected members had died of progressive renal disease with uremia. In addition, Sturtz and Burke [9] have recently reported two affected families in which the renal lesion and nerve deafness were progressive, leading to total loss of hearing and death early in adulthood in male members. The prognosis was less grave in their female patients.

The affected children in the family of our study (Cases 1 and 2) have been completely free of symptoms. The younger maternal uncle, who has been known to have hematuria for 15 years, has complained on occasion of low-back pain when the hematuria was severe. The older maternal uncle was known to have had hematuria for 15 years

prior to his death from renal disease at age 40. One patient reported by Reyersbach and Butler [1] had frequent and severe abdominal pain requiring repeated hospitalizations early in life. For the most part, however, it would appear that the abnormality has not been associated with significant symptoms during early life.

A large number of etiological factors have been recognized as being responsible for "asymptomatic" hematuria, and each deserves some consideration in the evaluation of patients such as have been considered here. The persistence of asymptomatic hematuria following anaphylactoid purpura has been discussed by Wedgewood et al.[5] Long-standing hematuria in patients with sickle-cell trait and other genetically controlled abnormalities in hemoglobin production has been described in recent years.[6] Reiman [7] has discussed cyclic bleeding with recurrent hematuria as a predominating symptom. Hemangiomata with bleeding in the urinary tract has long been recognized as a cause of hematuria. That the occurrence of such tumors may be genetically controlled makes the consideration of hemangiomata pertinent in any instances of familial hematuria.

Information is essentially nil regarding the responsible pathological alteration involved in the reported instances of idiopathic hereditary hematuria. Biopsy material from the kidney was obtained in one instance in Reyersbach's series. Anatomical alterations were limited to the presence of considerable numbers of erythrocytes in the convoluted tubules. Bowman's spaces were clear. Glomerular or vascular abnormalities could not be identified. It is regrettable that more extensive studies of glomerular and tubular function and biopsy material could not be obtained in the material reported here.

Summary

An unusual family has been described in which seven members in four generations (Figure) have been found to have hematuria which was asymptomatic in early life, but two of the family are known to have died of nephritis at ages 40 and 44 years. The known causes of hematuria have been excluded as being responsible for this finding in these persons.

The abnormality appears to be genetically transmitted as a dominant trait, transmitted in this one family by female members.

Female members affected appear to have less severe manifestations than affected males, which is in keeping with the limited observations of others.

The course of the disease does not appear to be entirely benign, although few symptoms other than hematuria have been present early in life.

The importance of differentiating these unusual instances of hematuria from glomerulonephritis and other known causes of this symptom is discussed.

We wish to extend our thanks to Dr. G. L. Wilkinson of South Boston, Va.; Dr. William S. Hooten of Lynchburg, Va., and Drs. Conrad Riley and Peter R. Scaglione of New York City for the information given to us from their medical records on the respective members of the family reported here.

910 Via de la Paz, Pacific Palisades, Calif.

REFERENCES

1. Reyersbach, G. C., and Butler, A. M.: Congenital Hereditary Hematuria, New England J. Med. 251:377-380, 1954.

2. Goodwin, W. E.; Alston E. F., and Semans, J. H.: Hematuria and Sickle Cell Disease, J. Urol. 63:79-96, 1950.

3. Alport, A. C.: Hereditary Familial Congenital Hemorrhagic Nephritis, Brit. M. J. 1:504-506, 1927.

4. Guthrie, L. G.: Idiopathic or Congenital Hereditary and Family Hematuria, Lancet 1:1243-1246, 1902.

5. Wedgewood, R. J. P., and Klaus, M. H.: Anaphylactoid Purpura: A Long Term Follow-Up Study with Special Reference to Renal Involvement, Pediatrics 16:196-207, 1955.

6. Chapman, A. L.; Reeder, P. S.; Friedman, J. A., and Baker, L. A.: Gross Hematuria in Sickle Cell Trait and Sickle Cell-Hemoglobin C Disease, Am. J. Med. 19:773-782, 1955.

7. Reiman, H. A., and de Barardinis, C. T.: Cyclic Disease, Medicine 30:219, 1951.

8. Rinkoff, S. S.; Stern, A., and Schumer, H.: Familial Nephritis, J. A. M. A. 113:661-664, 1939.

9. Sturtz, G. S., and Burke, E. C.: Syndrome of Hereditary Hematuria, Nephropathy, and Deafness, Proc. Staff Meet. Mayo Clin. 33:289-298, 1958.

Neonatal Hepatitis

ROY G. SHORTER, M.D.; ARCHIE H. BAGGENSTOSS, M.D., and GEORGE B. LOGAN, M.D., Rochester, Minn.

The presence of jaundice at birth or its onset early in the neonatal period may present formidable diagnostic difficulties to the pediatrician and to the pathologist, especially if the jaundice is prolonged and of the regurgitant form. If erythroblastosis fetalis is excluded, the differential diagnosis in most instances lies between congenital atresia of the bile ducts and neonatal (giant cell) hepatitis. Both these conditions have been the subject of studies in the literature,[1-15] and it is apparent that many clinical and biochemical similarities exist between the two conditions. As a result, exploratory laparotomy is commonly undertaken in such cases to assess the patency of the biliary tree, and wedges of tissue resected from the liver are supplied to the pathologist for histologic examination.

Since congenital atresia of the bile ducts and neonatal hepatitis are rare in clinical and pathologic practice, the purpose of this communication is to review the clinical and histologic records in seven cases of neonatal hepatitis seen at the Mayo Clinic during the period 1924 through 1957; through the courtesy of Dr. G. B. Kent, of St. Joseph's Hospital, Phoenix, Ariz., data are included on one patient from whom biopsy specimens were referred to one of us (A. H. B.) in 1958. The histologic features will be contrasted briefly with those seen in the noncirrhotic liver associated with congenital biliary atresia.

Submitted for publication Jan. 29, 1959.

Fellow in Pathology, Mayo Foundation (Dr. Shorter); Section of Pathologic Anatomy (Dr. Baggenstoss) and Section of Pediatrics (Dr. Logan), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Materials and Methods

The specimens of liver were fixed in formalin and, in some instances, in absolute alcohol. Sections 8μ thick obtained from tissue embedded in paraffin blocks were stained routinely with hematoxylin and eosin. Other staining techniques included Mallory's aniline blue and phosphotungstic acid method for connective tissue, Gomori's reticulin stain, Sudan black for lipids, and Best's carmine and the periodic acid-Schiff techniques (the latter with and without previous diastase digestion) for glycogen. Frozen sections of reserve material were cut and stained with Sudan IV for fat. Paraffin sections were stained by the Prussian blue technique for iron and by a ferric chloride-nitric acid method for bile pigment. In three instances, reserve material was not available and reports could be made only on sections stained with hematoxylin and eosin.

The cases of congenital biliary atresia were obtained from a review of the clinic records for the period 1924 through 1954. In only three of the 40 cases thus found was the liver not cirrhotic; therefore, these three cases were suitable for comparison on histologic grounds. The processing and staining in this group were identical with those used in the cases of neonatal hepatitis.

Results

The clinical findings in the eight cases of neonatal hepatitis are summarized in Table 1. Three representative cases will be described in detail. The histologic features in all cases will be considered subsequently. In two cases, the results of necropsy were available.

Report of Representative Cases

CASE 4.—A 3-month-old white girl was brought to the Mayo Clinic in 1950. She had been born at full term after an uneventful pregnancy and a short, spontaneous labor. Respiration was established naturally. The child was well until approximately one month after birth, when jaundice was noticed. The jaundice fluctuated in intensity from day to day. The child's stools had been light in color since birth; after the onset of jaundice, the urine had varied in color from light to dark amber.

TABLE 1.—*Clinical and Chemical*

Case	Sex	Age at Onset of Jaundice	Age on Adm. to Hospital	Fever	Hepato-megaly	Splenomegaly	Serum Bilirubin, Direct/ Indirect, Mg. per 100 Ml.	Stools
1	M	Few days	2 yr.	None	Present	Present	0/0.4	Normal
2	F	No jaundice	Newborn	None	Absent	Absent	--	--
3	F	3 days	4 mo.	None	Present	Present	4.6/1.4	Urobilinogen, 3.8 mg. in 24 hr.
4	F	1 mo.	3 mo.	None	Present	Absent	3.2/3.8	Urobilinogen present
5	F	1 mo.	1 mo.	None	Present	Absent	5.0/1.8	--
6	F	1 wk.	6 wk.	None	Absent	Absent	6.1/1.5	Urobilinogen present
7	F	1 mo.	3 mo.	101 to 105 F	Present	Absent	5.5/2.3	Urobilinogen absent
8	F	3 days	6 wk.	None	Present	Present	7.4/3.8	Urobilinogen absent

Two elder siblings were alive and well, and the parents were healthy, with no relevant past medical history. No evidence was present of significant blood-group incompatibility.

The child was jaundiced and poorly nourished, weighing 7¼ lb. (3,290 gm.). The liver was enlarged and smooth. The spleen was not palpable, and there were no other abnormal findings.

The results of hematologic examination were as follows: hemoglobin, 11 gm. per 100 ml. of blood; erythrocyte count, 3,480,000 per cubic millimeter of blood; leukocyte count, 17,400; differential percentages, normal; coagulation time (venous), 6 minutes (normal range of 6 to 10 minutes); bleeding time, 5½ minutes (normal of 3 minutes or less); platelet count, 294,000. The concentration of direct-reacting serum bilirubin was 3.2 mg. per 100 ml., and that of the indirect fraction was 3.8 mg. Bile was present in material obtained by duodenal drainage. Urinalysis revealed the presence of bile pigment but no urobilinogen.

Five days after admission, exploratory laparotomy was carried out. The liver was of normal appearance. The gallbladder was smooth and normal. Exploration for the common bile duct and hepatic ducts was not done. Cholecystogastrostomy and biopsy of the liver were performed. After the operation, the jaundice disappeared. At the last follow-up, in 1954, the child was normal apart from some slowness in speech development.

CASE 5.—A 1-month-old white girl was brought to the clinic in 1955. The mother had been hypertensive during the last trimester of the pregnancy but otherwise had been well. The child, a breech presentation, weighed 6¼ lb. (2,835 gm.) at birth and was not jaundiced. No significant blood-group incompatibility was found. One elder sibling had died at the age of 12 days, presumably from cerebral hemorrhage, but a necropsy had not been done. No family history of jaundice was present. When the child was 14 days old, the mother noticed that its abdomen was swollen and that the child was taking her feedings poorly.

Examination showed an absence of jaundice. The abdomen was swollen, and veins in the anterior abdominal wall were dilated. A fluid thrill was present. The liver was enlarged 4 cm. below the costal margin, and the spleen was not palpable.

Hematologic findings were as follows: hemoglobin, 11.7 gm.; leukocyte count, 8,400; differential percentages, normal; bleeding time, 5½ minutes; coagulation time, 30+ minutes; prothrombin time (Quick), 50 seconds (control, 18 seconds); platelet count, 152,000. The value for serum proteins was 3.6 gm. per 100 ml., with 2.5 gm. of albumin and 1.1 gm. of globulin. The cephalin-cholesterol flocculation test gave a 3+ reaction. The thymol-turbidity test gave a value of 1 unit. The serum peptidase measured 4.3 units. Urinalysis revealed Grade 2 albuminuria, and hyaline and granular casts. Roentgenographic examinations of the thorax and abdomen gave normal results; the calvarium was incompletely ossified, with the appearance of prematurity.

During the next day, the child became jaundiced and increasingly lethargic. The serum bilirubin at this time was 5 mg. direct and 1.8 mg. indirect. Bleeding from the nose and mouth occurred intermittently. Despite treatment, the baby died after severe hematemesis on the fourth day after admission.

Necropsy was done two hours after death. The body was 52 cm. in length (crown to heel) and weighed 3,590 gm. Severe jaundice was present. The abdomen was distended, and the veins in the

Data in Neonatal Hepatitis

Urine	Hemoglobin, Gm/100 Ml.	Quick Prothrombin Time, Sec. (Control 18 Sec.)	Serum Proteins, Gm/100 Ml.	Cephalin-Cholesterol Flocculation	Thymol Turbidity, Units	Bile Ducts, Operative or Necropsy Findings	Progress
Normal	11	19	Normal	Negative	--	Normal	Cirrhosis with esophageal varices
--	--	--	--	--	--	Normal	Died, age 72 hr.
--	9.8	--	--	--	6	Atresia?	Died, age 8 mo.
Bile pigment present	11	--	--	--	--	Ducts not searched for	Satisfactory
--	11.7	50	Total, 3.6; alb., 2.5; glob., 1.1	3+	1	Normal	Died, age 1 mo.
Bile pigment present	11.5	22	Total, 4.63; alb., 2.46; glob., 2.17	Negative	0	Normal	Cirrhosis
Bile pigment present	12.2	18	Total, 7.2; alb., 5.5; glob., 1.7	--	--	Biliary atresia?	Died, age 9 mo.
Bile pigment present	11.4	--	Total, 6.8; alb., 5.04; glob., 1.76	Negative	0	Normal	Common bile duct damaged at operation; jaundiced 2 mo. postoperatively

anterior abdominal wall were prominent. Edema of the periorbital tissues and the vulva was noted, and ecchymotic zones were seen in the skin of both groins. The peritoneal cavity contained 350 ml. of yellow fluid, and the pericardial sac contained 10 ml. of similar fluid. The liver was enlarged to 145 gm.; it was firm and green, and the surface showed fine granularity. The extrahepatic bile ducts were normal but were empty of bile. The gallbladder contained white fluid; a green calculus, 1 mm. in diameter, was present in the ampulla. No other abnormalities were noted in any system except for the presence of 15 ml. of black semifluid material in the stomach and duodenum, the mucosae of which, together with that of the esophagus, were normal. The spleen weighed 5 gm. and was normal in appearance.

Case 6.—A 6-week-old white girl was brought to the clinic in 1955. The child had had progressive jaundice for five weeks, associated with pale stools and dark urine. No evidence of significant blood-group incompatibility was found. The child had been delivered at term. The mother had been well during the pregnancy but had complained of itching during the last month. One older sibling was alive and well. The parents were in good health, with no history of jaundice. The mother's brothers had been jaundiced in childhood.

The child was well nourished and had moderate jaundice. No other abnormal physical signs were present.

Hematologic findings were as follows: hemoglobin, 11.5 gm.; leukocyte count, 10,600; differential percentages, normal; prothrombin time (Quick), 22 seconds (control, 18 seconds). The value for serum bilirubin was 6.1 mg. direct and 1.5 mg. indirect. The value for serum proteins was 4.63 gm., with 2.46 gm. of albumin and 2.17 gm. of globulin. The thymol-turbidity test gave a value of zero. A 24-hour sample of stool contained 0.3 mg. of urobilinogen. Urinalysis revealed the presence of bile pigment. Roentgenographic studies of the thorax and abdomen gave normal results.

Eight days after admission, exploratory laparotomy was performed. The liver appeared normal, and the extrahepatic bile ducts were present and patent; the cystic duct was extremely small. Cholecystectomy and biopsy of the liver were done.

The jaundice disappeared after operation. The child had a dramatic and short episode of coma but recovered rapidly. The coma was considered clinically to result from hepatic insufficiency. She eventually was dismissed from the hospital and has been studied at the clinic since that time. At the last visit, she had clinical evidence of cirrhosis, but further tissue from the liver has not been obtained for biopsy.

Summary of Clinical Data

Seven of the eight patients were girls; one (Case 7) was premature according to the birth weight. There were no significant features in the family histories except in Case 8, in which the mother gave a history of acute hepatitis three years before, and possibly in Case 1, in which a younger sibling also was jaundiced and an older sibling had been jaundiced after birth. Since histologic material from these siblings was not available, the full significance of this

history cannot be assessed. In four instances, the pregnancies had been uneventful; in Cases 1 and 5, mild toxemia had been present in the last month and the last trimester, respectively; in Case 6, the mother had complained of "itching" during the last month of her pregnancy; in Case 8, there had been vomiting in the first trimester.

The onset of clinically detectable jaundice in all seven cases in which jaundice was present was within the first month of life. In Case 2, jaundice was not present. In six cases, the serum concentration of direct-reacting bilirubin ranged between 3.2 and 7.4 mg. per 100 ml., and that for the indirect-reacting pigment was between 1.4 and 3.8 mg. No record of bilirubin determination was available in Case 2; in Case 1, the serum bilirubin was measured when the child was anicteric.

In three cases (3, 4, and 6), urobilinogen was present in the stools; in two (7 and 8), it was absent. There was no record of this investigation being carried out in Cases 2 and 5. In Case 1, the normal stool findings were noted at the time when jaundice was absent.

Bile pigment was present in the urine of four of the patients who were jaundiced when first seen. Records were not available in Cases 2, 3, and 5. It was absent from the urine in the nonicteric patient (Case 1).

The concentration of hemoglobin in the six jaundiced patients was between 9.8 and 12.2 gm. per 100 ml. of blood. Seven of the patients gave no evidence of significant blood-group incompatibility; the details in Case 2 were unavailable. Abnormalities in the leukocyte counts were not present in the jaundiced patients.

The Quick prothrombin times in Cases 5, 6, and 7 were 50, 22, and 18 seconds, respectively, the control time being 18 seconds in each instance. Bleeding from the nose and mouth was a pronounced feature in Cases 2 and 5; the latter patient had a terminal episode of hematemesis.

The concentration of serum protein revealed no points of diagnostic significance in any of the five jaundiced patients on whom this test was performed. The reactions in the cephalin-cholesterol flocculation test in Cases 5, 6, and 8 were 3+, negative, and negative, respectively. Results of the thymol-turbidity test in Cases 3, 5, 6, and 8, expressed in units, were 6, 1, 0, and 0, respectively.

Six of the patients (Cases 1, 3, 4, 5, 7, and 8) had clinical hepatomegaly; the spleen was palpable in Cases 1, 3, and 8.

The patency of the biliary tract was established at surgical exploration of the abdomen or at necropsy in five cases (1, 2, 5, 6, and 8) and was not established in one (Case 4). In Cases 3 and 7, the ducts were thought to be absent at the time of surgical exploration.

The subsequent progress of all the children showed a poor prognostic picture. At the time of last inquiry, two had hepatic cirrhosis (Cases 1 and 6) and four had died within 8 months of the onset of symptoms. One patient (Case 8) remained jaundiced two months after operation, but the significance of this is obscured by inadvertent damage to the common bile duct at operation. Only one child (Case 4) was apparently in good health.

Histologic Findings in Neonatal Hepatitis

Since the histologic appearances of the specimens of liver in these eight cases were fundamentally similar, they will be described together. Occasional differences will be mentioned. Six of the specimens were wedge sections obtained surgically and two were obtained at necropsy (Cases 2 and 5).

The general hepatic architecture in all the specimens was preserved. In Case 4, the reticulum framework showed patchy collapse and some evidence of proliferation of reticulum fibers. The portal tracts were infiltrated by inflammatory cells, but in no case was this infiltration a pronounced feature (Fig. 1, *a* and *b*). The type of cell was predominantly mononuclear, but some tracts contained occasional plasma cells, eosinophils, and lymphocytes. Eosinophils were

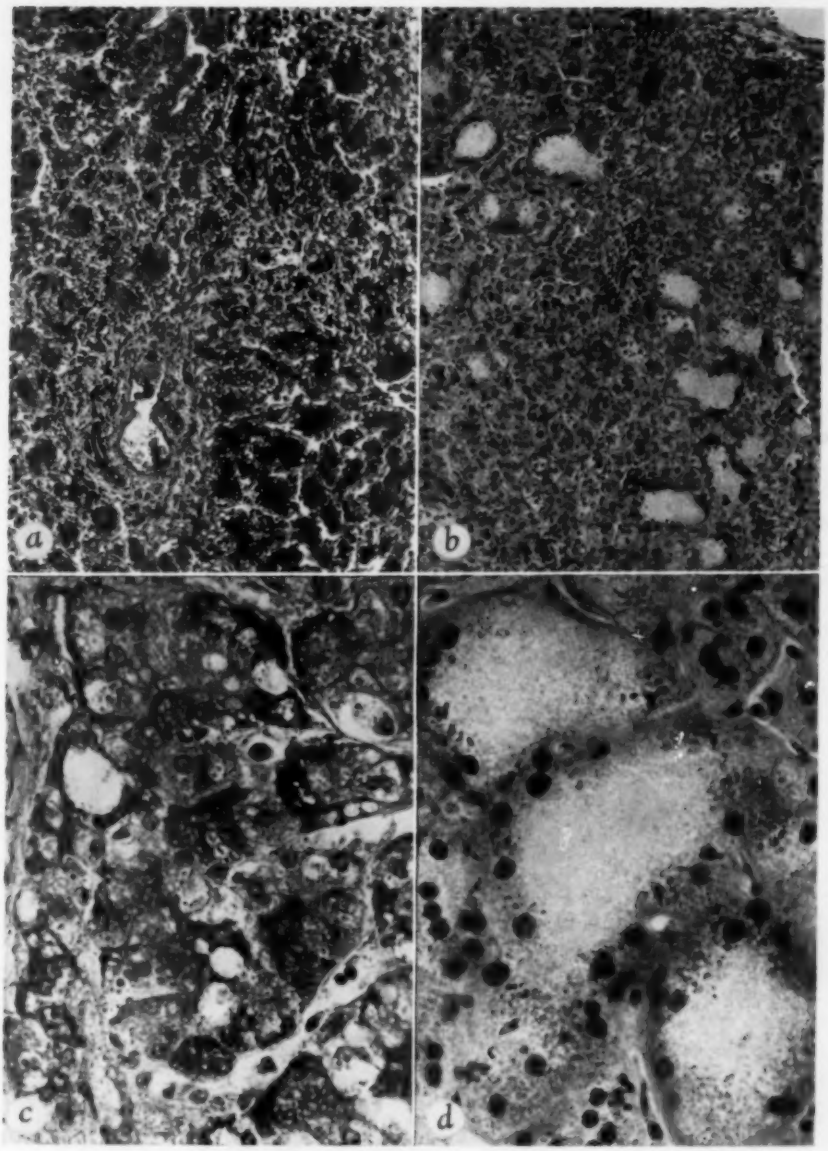


Fig. 1.—Neonatal hepatitis. (*a*) A portal tract is shown, demonstrating the paucity of inflammatory-cell response and the presence of fibroblastic proliferation. Giant cells are numerous (hematoxylin and eosin; × 100). (*b*) Numerous giant cells with clear central zones in the cytoplasm are present. The inflammatory response in the portal tract is slight (hematoxylin and eosin; × 100). (*c*) Giant cells containing glycogen (Best's carmine; × 400). (*d*) Giant cells with peripheral arrangement of nuclei, central zones of clear cytoplasm and peripheral eosinophilic cytoplasm. These particular cells contain intracytoplasmic bile pigment and iron (hematoxylin and eosin; × 450).

more numerous in Cases 4 and 5 than they were in the remainder; occasional segmented polymorphonuclear leukocytes were seen in the inflammatory-cell reaction in Cases 1, 4, and 5. Slight but atypical proliferation of true bile ductules in many portal tracts was a constant finding, but in no instance was this a prominent feature. Bile pigment was not seen in either the lumina or the epithelium of the bile ducts, and dilatation of the bile ducts was not present.

The blood vessels and lymphatic structures in the portal tracts showed no significant abnormalities. Numerous, small, dilated and congested blood vessels were noted around the larger bile ducts in Case 2. No structures that could be interpreted as cholangioles (canals of Hering) were observed in any of the cases except possibly in Case 4.

Fibroblastic activity with an increase in collagen was noted in the portal tracts in all cases, with small finger-like processes of fibroblastic activity in the adjacent parenchymal tissue (Fig. 1, *a*). This was especially pronounced in Case 2, in which connective tissue had joined the portal tracts and central veins in some zones.

The parenchyma of the liver showed the most dramatic changes. The degree of necrosis of the hepatic cells was not severe, being of patchy distribution and of lytic type with karyolysis and loss of cell structure. Little, if any, inflammatory reaction to the necrotic cells was present, and the few inflammatory cells seen in some zones were mononuclear. The distribution of the necrotic foci apparently was entirely random, with no predilection for central or periportal sites. Eosinophilic necrosis of hepatic cells was minimal and focal, being confined to solitary cells or groups of two or three cells. This eosinophilic degeneration was not associated with an inflammatory-cell reaction and also apparently was entirely random in distribution. Mitotic figures were not seen, and binucleate cells were not numerous.

The most obvious and impressive finding in the parenchyma was the occurrence of giant cells (Fig. 1, *a* and *c*). These cells varied in size, the smallest being two or three times the size of a normal parenchymal cell, whereas the largest was five or six times as large. The giant cells were multinucleate, the average number of nuclei being nine (based on counts of 100 cells in each case). The nuclei had varying sites of distribution, in some instances being arranged around the periphery of the cell, forming a complete or incomplete ring (Fig. 1, *d*); in others, they were arranged in a group at one pole of the cell, or in scattered distribution throughout the cytoplasm (Fig. 2). All forms were seen in each case. No significant

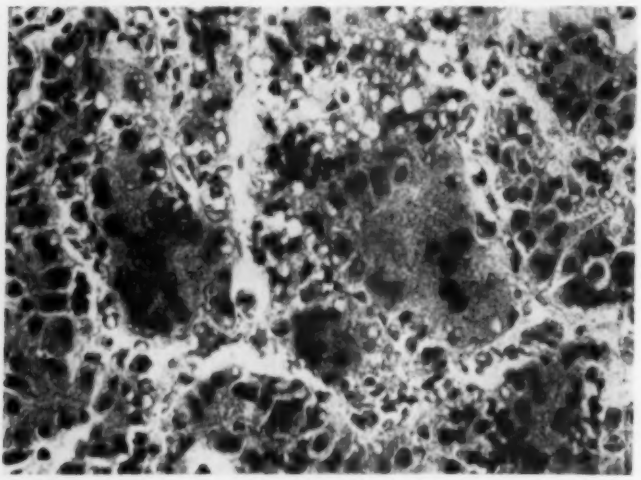


Fig. 2. — Giant cells showing different forms of nuclear arrangement and granules of bile pigment in the cytoplasm (hematoxylin and eosin; × 400).

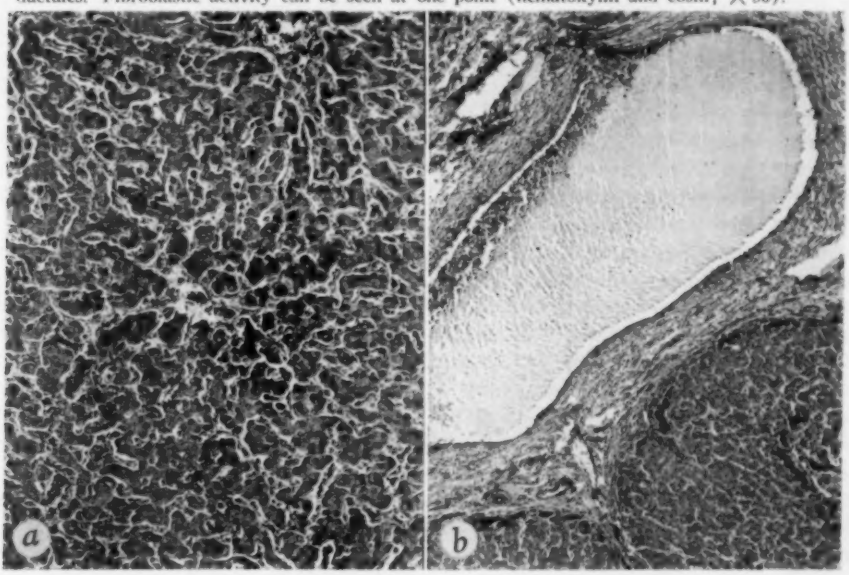
differences were noted in the size of nuclei when compared with that of nuclei of normal parenchymal cells, based on counts of 50 cells. The nuclei varied in appearance greatly within individual giant cells, ranging from those identical with normal nuclei to those with a homogeneous structure (Figs. 1, *d*, and 2). Mitotic figures were not seen, and karyolysis and karyorrhexis were absent. The cytoplasm of the giant cells most commonly was eosinophilic. The central zones of many giant cells were structureless and only a faint eosinophilic staining of this central zone could be seen, the more deeply eosinophilic cytoplasm assuming a ring-like arrangement around the periphery of the cell (Fig. 1, *d*). Large numbers of granules of bile pigment were present in the cytoplasm of the giant cells (Fig. 2); in some, the pigment had aggregated centrally to form microcalculi. These intracellular microcalculi, when associated with loss of the central cytoplasmic structure, gave to some giant cells the appearance of bile ductules containing bile plugs. Throughout the lobules, granules of bile pigment were present in surviving parenchymal cells and those showing lytic necrosis. Many of the giant cells were rich in cytoplasmic glycogen (Fig. 1, *c*), the other parenchymal cells containing variable amounts. No significant aggregations of lipids or neutral fat were seen in the cases in which reserve material was available for study.

There was no histologic evidence of nodular regeneration in any of the sections examined, but groups of hepatic cells forming pseudoducts at the periphery of portal tracts were seen in all cases.

The sinusoids showed no abnormalities except for foci of erythrogenesis in Cases 1 and 2. Kupffer cells were swollen and prominent in all the sections, particularly centrilobularly.

A few small bile plugs were seen in intercellular situations, but bile pigment was predominantly intracellular in location. In Case 4, true proliferation of atypical bile ductules was present within the lobules adjacent to the portal tracts, many of the atypical ductules containing bile plugs. This was the only case in which structures that

Fig. 3.—Congenital atresia of the bile ducts. (*a*) Centrilobular intercellular cholestasis in the hepatic parenchymal cells and Kupffer's cells (hematoxylin and eosin; × 100). (*b*) Portal tract, showing absence of inflammatory-cell reaction and inconspicuousness of bile ducts and ductules. Fibroblastic activity can be seen at one point (hematoxylin and eosin; × 50).



may represent the canals of Hering were observed. This true intralobular ductular proliferation was not found in the other cases, and these structures contrasted greatly with adjacent giant cells forming false ductular structures.

Special staining showed the presence of granules of iron within some of the giant cells in addition to bile pigment.

The central veins demonstrated fibroblastic activity in relationship to their walls. In Case 2, the fibroblastic activity extended peripherally from the central veins, with perisinusoidal formation of collagen.

Histologic Findings in Noncirrhotic Congenital Atresia

As already noted, the liver was not cirrhotic in only three of the 40 cases of congenital biliary atresia included in this study. The histologic features in these three examples were contrastingly different from those seen in neonatal hepatitis (Fig. 3).

The hepatic architecture in these three cases was preserved but damaged. Some increase was present in the fibrous tissue in the portal zones. Some portal tracts showed slight fibroblastic activity extending out into the parenchyma; these extensions appeared as small groups of fibroblasts apparently surrounding and proliferating between parenchymal cells. The inflammatory reaction in the portal tracts was minimal, and the few inflammatory cells present were mononuclear in type. No significant changes were seen in the bile ductules, and the vessels in the portal tracts were normal in appearance. Degeneration of hepatic cells varied from mild to severe, being predominantly eosinophilic in type in one case; lytic necrosis of cells was common to all cases. Inflammatory reaction to the necrotic cells was absent. Giant cells were not seen. Regenerative features were absent, as was pseudoductular formation by hepatic cells. The degree of cholestasis was less in these cases than it was in the examples of neonatal hepatitis, the bile pigment being both intracellular and intercellular in situation and predominantly centrilobular in distribution. No other significant abnormalities could be detected.

TABLE 2.—*Histologic Features in Neonatal Hepatitis and in Congenital Biliary Atresia Without Cirrhosis*

Feature	Neonatal Hepatitis *	Congenital Atresia of Bile Ducts (Noncirrhotic) †
Architectural damage	0 to ±	+
Portal tracts		
Proliferation of true bile ductules	+	0
Pseudoductular formation	+	0
Hepatic parenchymal cells		
Eosinophilic necrosis	0 to ±	+
Giant cell formation	++	0
Cholestasis (degree and distribution)	++; diffuse	+; predominantly central

* Age, 3 days to 1 month.
† Age, approximately 1 week.

The contrasting features between these findings and those of neonatal hepatitis are summarized in Table 2.

Comment

The occurrence of only eight proved cases of neonatal hepatitis in the records of the Mayo Clinic during a 34-year period emphasizes the comparative rarity of this disease. However, we have observed a number of infants on whom a presumptive diagnosis of hepatitis was made because they behaved clinically just as did the infants reported in detail in this paper. The only difference was that they made a complete recovery. Exploration or biopsy was not done because their jaundice fluctuated both clinically and chemically. The proved incidence at some other centers is certainly higher. Harris and associates [16] reported 30 cases seen in an eight-year period of what they described as parenchymal hepatic damage ("hepatitis"). Day [17] estimated that three new cases per year are seen at Kings County Hospital.

The clinical features of neonatal (giant cell) hepatitis are similar to those found in association with congenital biliary atresia. A comparison of the clinical data presented here with those in a review of congenital

biliary atresia by Myers and associates [14] serves to illustrate the lack of any clinical or biochemical specificity for either condition that can facilitate diagnosis and prevent unnecessary surgical exploration of some patients who have neonatal hepatitis. The histologic findings in our cases of neonatal hepatitis are in agreement with the descriptions given by Craig and Landing,[1] and by Dible and co-workers.[2] In one case in our series, however, extensive proliferation of true bile ductules of atypical form [18] was seen in an intralobular situation in addition to the other findings. The tissues in congenital atresia contrasted histologically in the distribution of cholestasis, by the absence of giant cells, and by the presence of large zones of eosinophilic necrosis.

The poor prognosis in our group of patients with neonatal hepatitis is in agreement with the findings of Stokes and associates,[10] and Craig and Landing. Gellis and co-workers,[5] however, noted that 29 (71%) of their 41 patients were alive and well after follow-up for periods of 6 months to 12 years, and Hsia and associates [20] stated that 60% of patients with neonatal hepatitis recover without sequelae.

From a survey of the literature, it is apparent that no conclusions have yet been reached on the pathogenesis of neonatal hepatitis. Stokes and co-workers, Craig and Landing, and Dible and associates favored transplacental viral infection as the probable mechanism, while Reiffenstuhl,[21] Zollinger,[22] and Zeitlhofer and Speiser [23] thought that blood-group incompatibility is the underlying cause of the disease. Hsia's group [20] described a possible hereditary component in the pathogenesis of the disease and indicated an autosomal recessive mode of inheritance.

Only one of our patients had a history of a previous attack of viral hepatitis in the mother, although the details available in Case 2 were incomplete. However, this does not exclude either previous anicteric hepatitis or the existence of a chronic carrier state for the virus of serum hepatitis in the maternal serum in the absence of any hepatic disease in the past. Gellis and associates [5] obtained a history of hepatitis in the mother in only 1 of 41 cases.

The absence of demonstrable evidence of significant blood-group incompatibility in seven of our patients does not exclude its existence, since results of the Coombs test may be negative in the presence of such incompatibility.[24] The concept that neonatal hepatitis may result from unrecognized blood-group incompatibility is supported by Krainin and Lapan [7]; Ehrlich and Ratner,[25] and Bain and co-workers [26] have suggested that some cases may result from unrecognized hemolytic disease. While seven of our patients were the offspring of multiparous mothers, a factor that might support the concept of an immune mechanism at work, none of the patients showed any definite evidence of hemolytic disease.

The histologic findings in our cases showed certain definite differences from the findings in viral hepatitis in older children or adults with respect to the degree and the distribution of necrosis, the formation of giant cells, and the inflammatory-cell reaction.

The significance of the formation of giant cells in neonatal hepatitis remains obscure. The eosinophilic staining of the cytoplasm suggests a degenerative process. Weisbrod and associates,[27] and Klemperer and co-workers [28] regarded the formation of multinucleate cells to be a manifestation of degeneration; however, it can be argued that formation of giant cells represents a form of exuberant regeneration, since Mann and Magath [29] observed that regeneration of the liver after partial hepatectomy is much more vigorous in young animals than it is in adults. The absence of mitotic figures in all the giant cells observed in this series does not exclude the possibility that active regeneration, perhaps amitotic in type, is occurring. Thaler [30] pointed out that mitotic division in typical viral hepatitis in adults occurs most frequently in the early stage of the disease before necrosis of hepatic cells is seen and does not appear to be a prominent feature

in regeneration after necrosis has occurred. It would appear plausible, therefore, that the formation of giant cells in the neonatal liver following injury may be a regenerative process and that the large number of these cells may illustrate the exaggerated power of the regenerative response of the infant liver.

Craig and Landing, who also commented on the histologic differences between their material and classic viral hepatitis, suggested that these findings may be related to the blood supply and differences in resistance to autolysis in the infant liver. It might be argued equally well that the differences exist because the underlying causes are not the same and that neonatal hepatitis is either not of viral origin at all or, at least, is not caused by the same organism, and that such similarities which do exist in the histologic findings between viral hepatitis in the adult and neonatal hepatitis result from the limited ability of the infant liver to respond to injury inflicted by different stimuli. It is possible that neonatal hepatitis is not an entity and that the clinical and histologic features indicate a limited range of hepatic cellular response to an assortment of stimuli, of which transplacental viral infection and blood-group incompatibility are examples. Janeway [31] also suggested this concept of neonatal hepatitis.

In our review of the material for this study, 30 samples of hepatic tissue from infants who had erythroblastosis fetalis due to Rh incompatibility were studied. The histologic picture in all these cases showed only large foci of extramedullary erythropoiesis and occasional foci of necrotic hepatic cells; in no instance were giant cells or cholestasis seen. Unless it is postulated that different blood-group incompatibilities produce different histologic appearances in the liver, this observation is against the concept of such incompatibilities as the factor responsible for neonatal hepatitis.

Summary and Conclusions

The clinical and histologic findings in eight cases of neonatal hepatitis are presented. The histologic features of neonatal hepatitis that contrast with the appearances seen in congenital atresia of the bile ducts are the formation of large numbers of multinucleated giant cells, the random distribution of cholestasis, together with the formation of microcalculi within the cytoplasm of the giant cells, and the absence of large areas of hepatic-cell necrosis. The possible significance of the formation of giant cells is discussed, and the theories of pathogenesis are reviewed. A common histologic response to different stimuli is postulated as a possible contributing factor to the difficulty of assessment of the pathogenesis.

Mayo Clinic.

REFERENCES

1. Craig, J. M., and Landing, B. H.: Form of Hepatitis in Neonatal Period Simulating Biliary Atresia, A. M. A. Arch. Path. 54:321-333 (Oct.) 1952.

2. Dible, J. H.; Hunt, W. E.; Pugh, V. W.; Steingold, L., and Wood, J. H. F.: Foetal and Neonatal Hepatitis and Its Sequelae, J. Path. & Bact. 67:195-206 (Jan.) 1954.

3. Schwartz, M. U.; Gilman, R. A.; Schwartz, M., and Settle, J.: Neonatal Hepatitis: Report of a Case Simulating Obstructive Jaundice, J. A. M. A. 155:557-559 (June 5) 1954.

4. Harris, R. C.; Andersen, D. H., and Day, R. L.: Obstructive Jaundice in Infants with Normal Biliary Tree, Pediatrics 13:293-307 (April) 1954.

5. Gellis, S. S.; Craig, J. M., and Hsia, D. Y.-Y.: Prolonged Obstructive Jaundice in Infancy: IV. Neonatal Hepatitis, A. M. A. Am. J. Dis. Child. 88:285-293 (Sept.) 1954.

6. Kiaer, W.: Hepatitis Foetalis, Ugesk. laeger 118:865-868 (July 26) 1956.

7. Krainin, P., and Lapan, B.: Neonatal Hepatitis in Siblings: Report of 2 Cases with Giant Multinucleated Liver Cells and Fatal Termination, J. A. M. A. 160:937-940 (March 17) 1956.

8. Thomson, J.: On Congenital Obliteration of the Bile Ducts, Edinburgh M. J. 37:523-531 (Dec.) 1891; 604-616 (Jan.); 724-735 (Feb.) 1892.

9. Holmes, J. B.: Congenital Obliteration of the Bile Ducts: Diagnosis and Suggestions for Treatment, Am. J. Dis. Child. 11:405-431 (June) 1916.

10. Ladd, W. E.: Congenital Atresia and Stenosis of the Bile Ducts, J. A. M. A. 91:1082-1085 (Oct. 13) 1928.

11. Sweet, L. K.: Congenital Malformation of the Bile Ducts: A Report of 3 Cases in 1 Family, J. Pediat. 1:496-501 (Oct.) 1932.

12. Gross, R. E.: The Surgery of Infancy and Childhood: Its Principles and Techniques, Philadelphia, W. B. Saunders Company, 1953.

13. Moore, T. C.: Congenital Atresia of the Extrahepatic Bile Ducts: Report of 31 Proved Cases, Surg., Gynec. & Obst. 96:215-225 (Feb.) 1953.

14. Myers, R. L.; Baggenstoss, A. H.; Logan, G. B., and Hallenbeck, G. A.: Congenital Atresia of the Extrahepatic Biliary Tract: A Clinical and Pathologic Study, Pediatrics 18:767-781 (Nov.) 1956.

15. Clatworthy, H. W., Jr., and McDonald, V. G., Jr.: The Diagnostic Laparotomy in Obstructive Jaundice in Infants, S. Clin. North America, pp. 1545-1554 (Dec.) 1956.

16. Harris, R. C.; Andersen, D. H., and Day, R. L.: Obstructive Jaundice in Infants with Normal Biliary Tree, Pediatrics 13:293-307 (April) 1954.

17. Day, R. L.: Personal communication to the authors.

18. Shorter, R. G.; Paton, A., and Pinniger, J. L.: Hepatic Jaundice, Quart. J. Med., to be published.

19. Stokes, J., Jr.; Wolman, I. J.; Blanchard, M. C., and Farquhar, J. D.: Viral Hepatitis in the Newborn: Clinical Features, Epidemiology, and Pathology, A. M. A. Am. J. Dis. Child. 82:213-216 (Aug.) 1951.

20. Hsia, D. Y.-Y.; Boggs, J. D.; Driscoll, S. G., and Gellis, S. S.: Prolonged Obstructive Jaundice in Infancy: V. The Genetic Components in Neonatal Hepatitis, A. M. A. J. Dis. Child. 95:485-491 (May) 1958.

21. Reiffenstuhl, G.: Infantile Lebercirrhose und ABO-Inkompatibilität, Schweiz. Ztschr. allg. Path. 16:197-209, 1953.

22. Zollinger, H. U.: Die biliäre Leberzirrhose im Säuglings- und Kleinkindalter und ihre Beziehung zum Morbus Haemolyticus Neonatorum, Helvet. paediat. acta 1 (Supp. 2):104-126, 1946.

23. Zeitlhofer, J., and Speiser, P.: Diffuse intraacinäre Lebercirrhose und Hydrops congenitus bei Rh-Incompatibilität, Oesterr. Ztschr. Kinderh. 5: 217-232 (Oct.) 1950.

24. Rosenfield, R. E.; Vogel, P., and Rosenthal, N.: The Antiglobulin Test: Technic and Practical Applications, Am. J. Clin. Path. 21:301-317 (April) 1951.

25. Ehrlich, J. C., and Ratner, I. M.: Congenital Cirrhosis of the Liver with Kernicterus: Report of 2 Cases in Siblings, with a Discussion of the Relationship to So-Called Neonatal Hepatitis and to Iso-Immunization Disease, Am. J. Path. 31:1013-1047 (Nov.-Dec.) 1955.

26. Bain, G. O.; Wang, G. C., and Misanik, L. F.: Giant Cell Hepatitis Associated with Hereditary Spherocytosis, J. Pediat. 51:549-553 (Nov.) 1957.

27. Weisbrod, F. G.; Schiff, L.; Gall, E. A.; Cleveland, F. P., and Berman, J. R.: Needle Biopsy of the Liver: III. Experiences in the Differential Diagnosis of Jaundice, Gastroenterology 14:56-72 (Jan.) 1950.

28. Klemperer, P.; Killian, J. A., and Heyd, C. G.: The Pathology of "Icterus Catarrhalis," Arch. Path. 2:631-652 (Nov.) 1926.

29. Mann, F. C., and Magath, T. B.: The Production of Chronic Liver Insufficiency, Am. J. Physiol. 59:485 (Feb.) 1922.

30. Thaler, H.: Zur Histologie der Virushepatitis, Schweiz. Ztschr. allg. Path. 16:129-155, 1953.

31. Janeway, C. A.: Discussion, New England J. Med. 258:553 (March 13) 1958.

The Natural History of Mental Deficiency in a State Hospital

II. Mentally Deficient Children Admitted to a State Hospital Prior to Their Sixth Birthday

GEORGE TARJAN, M.D.; STANLEY W. WRIGHT, M.D.; HARVEY F. DINGMAN, Ph.D., and GEORGES SABAGH, Ph.D., Pomona, Calif.

The physician must frequently advise parents on a long-term plan for the young, mentally deficient child. He is asked for help in their decision whether to place the child or keep him at home. Administrators of public institutions are under constant pressure to provide facilities for young patients, probably because there is a trend toward advising early placement. Only 2% of the Mongoloid patients admitted to Pacific State Hospital between 1945 and 1949 had been placed outside their homes shortly after birth; by 1955 this figure rose to 25%.[1] Of the patients on the present "waiting list" of Pacific State Hospital 41% are under 6 years of age. The same age group represents 11.4% of the Metropolitan Los Angeles population and 6.0% of the patients in the hospital.

Children who are admitted at an early age will differ in many respects from those who are admitted later in life. Responses to institutionalization will also vary with age. It is the purpose of this paper to acquaint physicians and administrators with selected characteristics of these patients and their families, and to indicate something of the hospitalization history of young patients. The paper compares data on mentally deficient children admitted to Pacific State Hospital prior to their sixth birthday with those obtained on patients who were admitted after that age. The material is based on experience with the first admissions to Pacific State Hospital during the period of July 1, 1948, to June 30, 1952. Basic information on the entire group was reported in previous publications.[2,3]

Methods

Pacific State Hospital is a California state facility for the treatment and care of the mentally deficient. There were 1,169 first admissions between 1948 and 1952, with an average daily population of approximately 1,900. Four hundred sixty patients were excluded from the study because (1) they were admitted for observation only; (2) they were immediately transferred to another state hospital; (3) they were diagnosed as not mentally deficient, or, (4) they left the hospital without authorization.

Submitted for publication Feb. 6, 1959.

Presented in part before the "Visiting Lecturer Series" of the Psychiatric Institute of the University of Nebraska College of Medicine, Omaha, October, 1958.

Supported in part by the National Institute of Mental Health Grant No. 3M-9130: Population Movement of Mental Defectives and Related Physical, Behavioral, Social, and Cultural Factors. Pacific State Hospital, Pomona, California.

Superintendent and Medical Director, Pacific State Hospital, and Associate Clinical Professor, Department of Psychiatry, School of Medicine, University of California, Los Angeles (Dr. Tarjan); Assistant Professor, Department of Pediatrics, School of Medicine, University of California, Los Angeles, and Research Consultant, Pacific State Hospital (Dr. Wright); Project Director, Population Movement Study, Pacific State Hospital, and Research Associate, Department of Psychiatry, School of Medicine, University of California, Los Angeles (Dr. Dingman); and Research Sociologist, Population Movement Study, Pacific State Hospital, and Associate Professor, Department of Sociology, University of Southern California (Dr. Sabagh).

There remained 709 admissions.* Of these, 170 patients were less than 6 years of age at the time of admission. They comprise the primary population of this report and are compared with 539 patients who were past their sixth birthday at the time of admission. The majority of the patients came from Metropolitan Los Angeles, and, where applicable, comparisons were made with the population of that area from data supplied in the 1950 United States Census reports.[4]

The patients were studied for age at admission; sex; clinical diagnosis; intelligence quotient; the presence of selected handicaps, and race. The homes were reviewed for intactness. The parents were examined for their educational, intellectual, and occupational levels, and their marital status. The information was obtained from the patients' clinical records, was coded, and transferred onto punch cards for further analysis. Each patient was followed for a four-year period after admission to determine the probability of death in the hospital, or the likelihood of live release.

The data are presented in tabular form, with footnotes on the statistical significance of the findings. These were obtained by the χ^2 method.[5,6] The age groups 0 to 6 years, and 6 years and over were compared with one another and/or the Metropolitan Los Angeles census figures for the total tabulations. No comparisons were made between subunits such as a single subdiagnosis, a specific educational level, etc.

* The discrepancy from the sample in the previous publications was the result of the exclusion in this publication of patients who left the hospital without authorization.

TABLE 1.—*Age Distribution of Patients Admitted to Pacific State Hospital Prior to Sixth Birthday, 1948-1952*

Age at Admission, Yr.	Number	Percentage
0 to 2	30	18
2 to 3	37	22
3 to 4	33	19
4 to 5	38	22
5 to 6	32	19
Total	170	100%

Results

Table 1 presents the age distribution of the patients admitted prior to their sixth birthday. Facilities for the care of infants are usually not available; hence, only two children under one year of age were admitted. Patients between their first and sixth birthdays are represented evenly in each age group.

Patients admitted prior to or after their sixth birthday are compared by sex in Table 2. Significant differences are not found. Males outnumber females at the approximate ratio of 4:3 in both age groups. The total population of the hospital shows a similar sex ratio. In comparison to the Metropolitan Los Angeles area, the number of males are greater in both groups, particularly among the older patients.

In Table 3 the admission diagnoses of the two groups are compared. The criteria of the Statistical Manual of the American

TABLE 2.—*Sex by Age*: First Admissions, Pacific State Hospital, 1948-1952*

Sex	Number			Percentage			Los Angeles Standard Metropolitan Area (1950), %	
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total	0 to 6	6 & Over
Male	99	308	407	58.0	57.0	57.4	50.9	48.0
Female	71	231	302	42.0	43.0	42.6	49.1	52.0
Total	170	539	709	100.0	100.0	100.0	100.0	100.0

* The 0 to 6 group is not statistically different from the 6 and over group; the 0 to 6 group differs from the Metropolitan Los Angeles Census group beyond the 5% level; the 6 and over group differs from the Metropolitan Los Angeles Census group beyond the 1% level.

TABLE 3.—*Diagnosis by Age*: First Admissions, Pacific State Hospital, 1948-1952*

Diagnosis	Number			Percentage		
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total
Familial	7	97	104	4.1	18.0	14.7
Undifferentiated	24	180	204	14.1	33.4	28.8
Mongolism	36	31	67	21.2	5.8	9.4
With developmental cranial anomaly	31	20	51	18.2	3.7	7.2
With congenital cerebral spastic infantile paraplegia	7	23	30	4.1	4.3	4.2
Due to infection	16	58	74	9.4	10.8	10.4
Due to trauma during birth	30	76	106	17.7	14.1	14.9
Due to trauma after birth	1	16	17	0.6	3.0	2.4
Due to epilepsy	2	16	18	1.2	3.0	2.5
All others	16	20	36	9.4	3.7	5.1
Unknown	0	2	2	0.0	0.4	0.3
Total	170	539	709	100.0	100.0	100.0

* Significant beyond the 1% level of probability.

Association on Mental Deficiency are used.[7] The term "Familial" is used when there are other mentally deficient individuals in the patient's immediate family, and when no other diagnosis is deemed appropriate. "Undifferentiated" is a category used for patients for whom no other classification is considered proper. The "Due to epilepsy" group includes patients in whom epilepsy and mental deficiency coexist without identifiable cause for either condition. "All others" includes patients with infrequent types of mental deficiencies such as tuberous sclerosis, familial amaurosis, or other organic nervous diseases.

Clinical entities of mental deficiency associated with physical stigmata are found more frequently in the younger age group. Mongolism and developmental cranial anomalies, e. g., hydrocephaly or microcephaly, constitute 39.4% of the diagnoses in these patients. In contrast, the diagnostic categories of familial and undifferentiated represent 51.4% of the patients in the older group. The frequencies of the other diagnoses are nearly equal.

The intelligence quotients, obtained at admission, are compared in Table 4. They represent the results of tests deemed most appropriate by the examining psychologist for the general developmental level of the patient. Deficiencies in the younger age group are severer; 95% had an IQ below 50, as compared with 53.4% in the older group.

On admission, 39.4% of the younger children had a history of seizures, in contrast to only 27.1% of the older group (Table 5). Some patients with a positive history were not found to have seizures after admission; seizures were verified during the four-year follow-up period in only 25.3% of the younger, and 22.1% of the older patients.

TABLE 4.—*Intelligence Quotient by Age*: First Admissions, Pacific State Hospital, 1948-1952*

Intelligence Quotient	Number			Percentage		
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total
0-19	100	110	210	59.0	20.0	29.6
20-49	62	180	242	36.0	33.4	34.1
50 and over	8	249	257	5.0	46.6	36.3
Total	170	539	709	100.0	100.0	100.0

* Significant beyond the 1% level of probability.

TABLE 5.—*History of Epilepsy by Age*: First Admissions, Pacific State Hospital, 1948-1952*

Epilepsy	Number			Percentage		
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total
Positive history	67	146	213	39.4	27.1	30.0
Negative history	102	392	494	60.0	72.7	69.7
Unknown	1	1	2	0.6	0.2	0.3
Total	170	539	709	100.0	100.0	100.0

* Significant beyond the 1% level of probability.

Each patient was reviewed to determine whether, at the time of admission, he had a visual, hearing, or major neuromuscular handicap; whether he was able to speak, and whether he was toilet trained. Severe intellectual impairment often interfered with accurate evaluation; therefore, simplified, practical criteria were used. Decisions were based on the history given by the parents, and on the observations of the physicians and nursing personnel. The judgments of these groups represented the degree to which the patient was dependent on nursing care. A "visual handicap" indicated that, with or without glasses, the patient was unable to see persons or large objects. A "hearing difficulty" was defined as that degree of impairment which interfered with hearing of ordinary voice sounds, such as simple commands or directions. No attempt was made to separate functional from organic hearing defects. Patients who required support, or could not walk at all, were considered to have a "major difficulty" in the use of the lower extremities. The function of the arms and hands was judged similarly by their use in feeding and dressing. "Major difficulty" in speech was defined as being generally unintelligible except for a few words or brief phrases. A patient was considered not toilet trained when "keeping him on schedule" did not prevent frequent wetting and soiling.

As may be seen in Table 6, visual and hearing difficulties were found nearly twice as often in the younger age group. The difference in the impairment of the extremities was even greater; 69.4% of the younger patients could not walk, as compared with only 14.5% of the older group. Major difficulties in the use of the arms and hands were present in 86.5% of the 0 to 6 age group, as compared to 20.8% in the older group; 96.5% of the young patients could not indicate their needs, wants, or desires through verbal means, in contrast to only 34.1% of the older group. Among the younger patients, 87.1% were not toilet trained; the comparable figure in the older patients was 17.3%. In many patients the degree of handicap changed during the

TABLE 6.—*Selected Major Physical Handicaps by Age*: First Admissions, Pacific State Hospital, 1948-1952*

	Number			Percentage		
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total
Total patients	170	539	709	24.0	76.0	100.0
Visual handicap	77	145	222	45.3	26.9	31.3
Hearing difficulty	44	93	137	25.9	17.3	19.3
Major difficulty in walking	118	78	196	69.4	14.5	27.6
Major difficulty in arm and hand use	147	112	259	86.5	20.8	36.5
Major speech difficulty	164	184	348	96.5	34.1	49.1
Lack of toilet training	148	93	241	87.1	17.3	34.0

* Significant beyond the 1% level of probability.

TABLE 7.—*Race by Age*: First Admissions, Pacific State Hospital, 1948-1952*

Race	Number			Percentage			Los Angeles Standard Metropolitan Area (1950), % †	
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total	0 to 6	6 & Over
Whites (excluding Mexicans)	150	372	522	92.0	72.2	77.0	84.1	88.2
Mexican-American	7	94	101	4.3	18.3	14.9	10.3	6.8
Negro	6	49	55	3.7	9.5	8.1	5.6	5.0
Other and unknown	7	24	31	Not included in rates to simplify comparison with Metropolitan Los Angeles				
Total	170	539	709	100.0	100.0	100.0	100.0	100.0

* The 0 to 6 group differs from the 6 and over group beyond the 1% level of significance; the 0 to 6 group differs from the Metropolitan Los Angeles group at the 2% level; the 6 and over group differs from the Metropolitan Los Angeles group beyond the 1% level.

† Age distribution for nonwhites was used to estimate population in age groups 0 to 6 and 6 and over for Negroes and Mexican-Americans.

four-year follow-up period. These changes will be reported in subsequent publications.

When the patient groups are compared by race it is found that the minority groups are represented less frequently among the younger patients and more frequently among the older ones. The findings are the same whether the groups are compared with each other, or with the population of the Metropolitan Los Angeles area (Table 7).

The parents are compared on selected sociocultural factors. The results are presented in Tables 8, 9, 10, and 11. The guardian is defined as the major wage earner in the patient's family. Miner's classification estimates the intelligence distribution of adults by occupation; Hollingshead's classification groups occupations by their prestige and the skills they require.[8,9] Comparisons are made between the groups and the Metropolitan Los Angeles population. In Table 10 Miner's original population distribution is used for comparison.

The results are similar with each approach. The parents of the young patients represented a cross section of the general population in educational, vocational, or social background. The parents of the patients admitted at an older age showed a lower level of education, intelligence, and social status as compared with the general population and parents of the younger children. Similar observations were made previously.[10]

TABLE 8.—*Education of Father by Patient's Age*: First Admissions, Pacific State Hospital, 1948-1952*

Years of Schooling	Number			Percentage			Los Angeles Standard Metropolitan Area (1950), % †
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total	
Grammar school	28	224	252	18.5	52.6	43.7	22.9
High school but not completed	26	57	83	17.2	13.4	14.4	20.2
High school graduate	53	87	140	35.1	20.4	24.2	30.2
College but not graduated	27	33	60	17.9	7.7	10.4	15.4
College graduate	17	25	42	11.3	5.9	7.3	11.3
Unknown	19	113	132	Not included in rates to simplify comparison with Metropolitan Los Angeles			
Total	170	539	709	100.0	100.0	100.0	100.0

* Fathers of the 0 to 6 group differ from those of the 6 and over group beyond the 1% level; the fathers of the 0 to 6 group do not differ from comparable age groups of the Metropolitan Los Angeles males; the fathers of the 6 and over group differ from the Metropolitan Los Angeles males beyond the 1% level.

† Males, ages 25-54.

TABLE 9.—*Education of Mother by Patient's Age*: First Admissions, Pacific State Hospital, 1948-1952*

Years of Schooling	Number			Percentage			Los Angeles Standard Metropolitan Area (1950), % †
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total	
Grammar school	25	204	229	15.3	46.0	37.8	19.9
High school but not completed	28	77	105	17.2	17.4	17.3	20.6
High school graduate	72	113	185	44.2	25.5	30.5	37.5
College but not graduated	26	34	60	16.0	7.7	9.9	14.2
College graduate	12	15	27	7.3	3.4	4.5	7.8
Unknown	7	96	103	Not included in rates to simplify comparison with Metropolitan Los Angeles			
Total	170	539	709	100.0	100.0	100.0	100.0

* Mothers of the 0 to 6 group differ from those of the 6 and over group beyond the 1% level; the mothers of the 0 to 6 group do not differ from comparable age groups of the Metropolitan Los Angeles females; the mothers of the 6 and over age group differ from the Metropolitan Los Angeles females beyond the 1% level.

† Females, ages 25-54.

TABLE 10.—*Guardian's Intelligence by Patient's Age (Miner's Classification)*: First Admissions, Pacific State Hospital, 1948-1952*

Classification	Number			Percentage		
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total
Top 12.2% of IQ distribution	17	27	44	11.4	6.2	7.5
Upper middle 31.7% of IQ distribution	41	107	148	27.5	24.4	25.2
Lower middle 38.4% of IQ distribution	68	167	235	45.1	38.1	40.0
Lower 17.7% of IQ distribution	23	137	160	15.4	31.3	27.3
No occupation, housewife, and unknown	21	101	122	Not included in rates to simplify comparison		
Total	170	539	709	100.0	100.0	100.0

* Guardians of the 0 to 6 age group differ from those of the 6 and over group beyond the 1% level; the guardians of the 0 to 6 group do not differ from Miner's distribution; the guardians of the 6 and over age group differ from Miner's distribution beyond the 1% level.

TABLE 11.—*Guardian's Occupation (Hollingshead's Classification) by Patient's Age*: First Admissions, Pacific State Hospital, 1948-1952*

Occupations	Number			Percentage			Los Angeles Standard Metropolitan Area (1950), % †
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total	
White collar	74	117	191	49.6	26.7	32.5	32.9
Skilled and semiskilled	57	213	270	38.3	48.5	45.9	36.4
Unskilled	18	109	127	12.1	24.8	21.6	10.7
Unknown	21	100	121	Not included in rates to simplify comparison with Metropolitan Los Angeles			
Total	170	539	709	100.0	100.0	100.0	100.0

* The 0 to 6 group is statistically different from the 6 and over group at the 1% level; the 6 and over group is statistically different from the Metropolitan Los Angeles figures at the 1% level; the 0 to 6 group is not statistically different from the Metropolitan Los Angeles figures.

† Estimated by using census tabulation on occupation by income for males age 14 and over.

TABLE 12.—*Intactness of Home by Age of Patient*: First Admissions, Pacific State Hospital, 1948-1952*

	Number			Percentage			Los Angeles Standard Metropolitan Area (1950), % †
	0 to 6	6 & Over	Total	0 to 6	6 & Over	Total	
"Parents" not living together	33	169	202	19.5	31.5	29.6	8.9
"Parents" living together	136	368	504	80.5	68.5	71.4	91.1
Unknown	1	2	3	Not included in rates to simplify comparison with Metropolitan Los Angeles			
Total	170	539	709	100.0	100.0	100.0	100.0

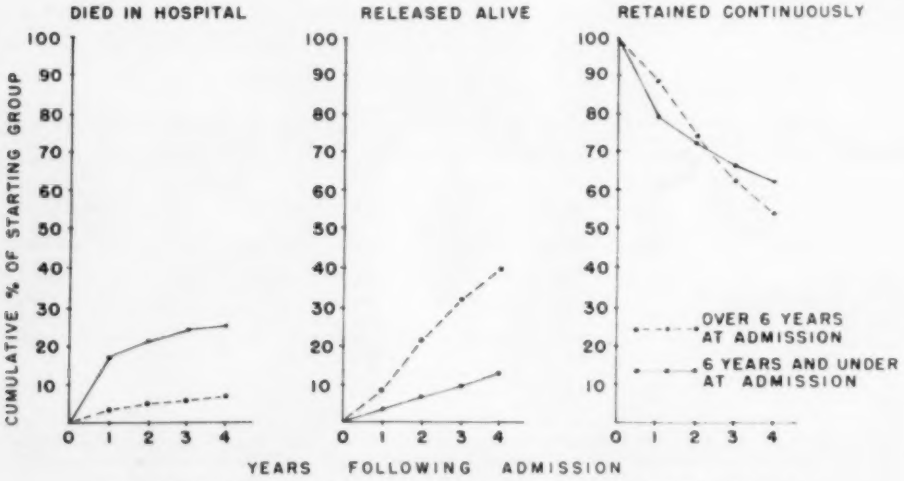
* Significant beyond the 1% level of probability.
† Only families with children under 18 years of age are included.

Statistically significant differences were not found in the frequency of the diagnosis of mental deficiency in the parents of the two groups; 2% of the fathers of the young children and 1.8% of the fathers of the older children had this diagnosis. The comparable figures for the mothers were 2.4% for the younger, and 5% for the older group. Comparative data are not available for the general population.

The histories were reviewed concerning the marital status of the biological parents. Significant differences were not found between the two groups; 11% of the younger patients and 10% of the older ones were illegitimate. Comparative figures for the general population were not available.

The "intactness" of the patient's last home setting was also studied. "Parents" for this purpose were defined as the biological, foster, or adoptive parents, or any other adult figures who were assuming care of the patient. As may be noted in Table 12, the frequency of broken homes was greater in both groups than in the general population. This difference was more marked for the older age group than for the younger one.

The graph compares the likelihood of death, live release, and continuous retention in the two groups. A four-year follow-up period was used. "Live release" was defined as the first release of the patient from the hospital, with the intent that he not



Hospitalization history by age: first admissions, Pacific State Hospital, 1948-1952.

return. Only the first "change of status" was counted, and readmitted patients were not reentered into the sample.

Mortality was much higher in the younger age group, particularly during the first year of hospitalization; 17.6% of the younger patients died within one year, in contrast to 3.7% of the older group. The difference was less striking after the first year. The likelihood of live release was much lower for the younger patients; only 12.9% were released in four years, against 39.5% in the older group. The young population group became rapidly depleted during the first year through its high mortality. After the first year there was a greater likelihood for the young patients to remain in the hospital during the four-year follow-up period because mortality decreased and the likelihood of release did not significantly increase.

Comment

Seven hundred nine patients admitted to Pacific State Hospital between 1948 and 1952 were studied. The patients were divided into two groups according to age on admission; the criterion of 6 years was used so that young patients could be compared with those who were admitted at an older age. The other characteristics were examined against the fixed criterion of age on admission. Significant differences were found between the young population group and the older patients. The material presented is part of a major study concerned with characteristics of hospitalized mentally deficient patients, and with the factors which produce hospitalization, improvement and release, and posthospital adjustment. Many other variables are under study in addition to those presented in this paper. They will be the subjects of future reports.

The data described here were compiled to obtain information on patients admitted at a young age to a state hospital, and no "causative" role can be attributed to age on the basis of these findings. Several of the variables besides age may have produced the observed differences. As an example, it was noted that the parents of patients admitted at a younger age represented a cross section of the general population, whereas the parents of the older ones generally came from a lower educational, occupational, and social background. The younger patients, however, were also found to be more deficient, and this degree of deficiency could also account for the observed differences in the parents; in fact, in another analysis to be published later, it was noted that the parents of the more deficient hospitalized patients resembled the parents of the younger group, and the parents of the less deficient patients compared with the older group. Clinical diagnosis, if used as a fixed criterion, may also produce similar results. Since only hospitalized patients were utilized in the study, no conclusions can be drawn concerning any cause and effect relationship between parental characteristics and the type or degree of deficiency observed in the child.

The observations were made on patients who were admitted to Pacific State Hospital between 1948 and 1952; therefore, the results are not directly applicable to patients who were admitted to another hospital, or to patients who will enter Pacific State Hospital at a later date. The characteristics of patients admitted to a state institution, and the outcome of their hospitalization, depend upon many factors, among them the program of the hospital, the availability of community facilities, and attitude toward institutionalization.

The observations, however, suggest the following general description for patients who are to be admitted to a state hospital before their sixth birthday: they are more likely to be boys; their mental defect is often associated with observable physical signs; 19 out of 20 times they have an IQ of less than 50; superimposed physical handicaps of a visual, auditory, neuromuscular, or convulsive nature are common in them; they rarely have significant speech development; nor are they toilet trained. They are more likely to come from the major racial group. Their parents will tend

to resemble the adult general population of the community in educational, occupational, or social status.

Following admission, a stormy early hospital adjustment can be expected, with a high first-year mortality. The 17.9% first-year mortality of this study group should be reemphasized, even though in a comparable age group admitted to Pacific State Hospital only four years later, between July 1, 1956, and Nov. 30, 1957, the first-year mortality dropped to 9.09%. The probability of release is limited for these patients admitted at a young age; approximately 3% of the original group leave the hospital during each of the first four years. In counseling parents on a long-range program for the young, mentally deficient child, the physician should, therefore, call attention to the high early mortality and to the continued probability of discharge.

Summary

Selected data are presented on mentally deficient patients who were admitted to a state hospital prior to their sixth birthday. They were followed for a four-year period after admission and were compared with those patients who were admitted after the age of 6 years. The young patients were found to be more severely deficient, with more superimposed handicaps than the older ones. Their mortality rate was high during the first year of hospitalization, with only a low probability for discharge during the first four years of hospital life. Their families resembled a cross section of the adult general population. These findings should prove useful to physicians in their counseling of parents, and to hospital administrators in their planning of programs.

Appreciation for assistance is expressed to the Western Data Processing Center, Division of the Graduate School of Business Administration, University of California, Los Angeles.

Pacific State Hospital, Box 100.

REFERENCES

1. Centerwall, S. A., and Centerwall, W. R.: Personal communication to the authors, 1958.

2. Kramer, M.; Person, P. H., Jr.; Tarjan, G.; Morgan, R., and Wright, S. W.: A Method for Determination of Probabilities of Stay, Release, and Death, for Patients Admitted to a Hospital for the Mentally Deficient: The Experience of Pacific State Hospital During the Period 1948-1952, Am. J. Ment. Deficiency 62:481-495 (Nov.) 1957.

3. Tarjan, G.; Wright, S. W.; Kramer, M.; Person, P. H., Jr., and Morgan, R.: The Natural History of Mental Deficiency in a State Hospital: I. Probabilities of Release and Death by Age, Intelligence Quotient, and Diagnosis, A. M. A. J. Dis. Child. 96:64-70 (July) 1958.

4. U. S. Census of Population 1950, U. S. Bureau of the Census, Vol. 2: Characteristics of the Population, Pt. 5, California, 1952; Vol. 4: Special Reports, Pt. 3, Persons of Spanish Surname, 1953; Vol. 4: Special Reports, Pt. 3, Non-White Population by Race, 1953; Vol. 4: Special Reports, Pt. 2, General Characteristics of Families, 1956.

5. Cochran, W. G.: Some Methods for Strengthening the Common Chi Square Tests, Biometrics, pp. 417-451, Dec., 1954.

6. Guilford, J. P.: Fundamental Statistics in Psychology and Education, Ed. 3, New York, McGraw-Hill Book Company, 1956.

7. Statistical Manual for the Use of Institutions for Mental Defectives, Ed. 3, American Association on Mental Deficiency, in cooperation with the National Committee for Mental Hygiene, Utica, N. Y., State Hospitals Press, 1946.

8. Miner, J. B.: Intelligence in the United States, New York, Springer Publishing Company, Inc., 1957.

9. Hollingshead, A. B.: Two Factor Index of Social Position, New Haven, Conn., printed privately, 1957.

10. Paterson, D. G., and Rundquist, E. A.: The Occupational Background of Feeble-Mindedness, Am. J. Psychol. 45:118-124, 1933.

Case Reports

Mima Polymorpha Meningitis

Report of Case and Review of the Literature

COMDR. CHARLES L. WAITE (MC), U. S. N., and LT. ALLEN H. KLINE (MC), U. S. N. R.

The micro-organism Mima polymorpha was first isolated in 1939 by DeBord [1] from the urethral discharge of patients being studied for resistant gonorrhea. This Gram-negative rod, with a marked tendency to pleomorphism, was aptly named by him because of its ability to mimic other Gram-negative bacteria, particularly those of the Neisseria genus. M. polymorpha remained primarily the interest of the bacteriologist until 1948, at which time DeBord [2] reported a case of meningitis in which this micro-organism was identified in the cerebrospinal fluid. Since then there have been five reported cases of meningitis due to M. polymorpha,[3-6] but only one of these occurred in a patient of the pediatric age group.[3]

The purpose of this case report is to call the attention of those caring for children to this micro-organism as an etiologic agent in meningitis, emphasizing its ability to mimic other infections and the variability of findings from case to case and to discuss the treatment of choice.

Report of Case

A 6-year-old white girl was admitted to the U. S. Naval Hospital on Sept. 7, 1958, with the chief complaints of abdominal pain and stiff neck. She had become ill four days prior to admission and was seen in the outpatient department of the hospital at that time. During her initial visit, the chief complaint was pain in the abdomen centering around the umbilicus. Other than a temperature of 100 F. (r), the physical findings were normal and no specific therapy was recommended. The patient was seen again as an outpatient on Sept. 7, 1958, with a stiff neck in addition to the abdominal pain and a temperature of 102 F (r). She was admitted for diagnosis and treatment. Physical examination on admission revealed an acutely ill child in an opisthotonic posture, complaining of severe aching in her abdomen, back, and neck. She was of normal size for her age, weighing 42 lb. Her blood pressure was 80/56; pulse rate 118; respiratory rate 26, and temperature 102.2 F (r). There was no altered state of consciousness. No exanthem or enanthem was present. The positive findings were limited to the neurological examination. In addition to the previously described opisthotonus, the patient exhibited marked stiffness of the neck and vigorously resisted any attempt to flex it. The Kernig and Brudzinski signs were positive. The cranial nerves were intact, and the fundi were normal. The superficial and deep tendon reflexes were equal and somewhat diminished. The Babinski response was normal. The initial clinical impression was that the patient had meningitis.

The white blood cell count on admission was 8,800, with a differential of 54% neutrophiles, 43% lymphocytes, and 3% monocytes. The hemoglobin was 10.4 gm. % and the hematocrit was 35. The urinalysis was normal. The initial spinal tap on Sept. 7 showed clear fluid, with an opening pressure of 80 mm. of CSF. No cells or bacteria were noted on the smear. The protein was 18 mg/100 cc., and the sugar was 51 mg/100 cc. Some of the fluid was placed in culture media.

The unexpected finding of a clear spinal fluid with no cells or bacteria influenced the clinical diagnosis, which now was that of an early aseptic meningitis possibly due to an ECHO or Coxsackie virus. Blood cultures and an acute phase serum were drawn. The patient was treated symptomatically. Eighteen hours later the laboratory reported a rapidly growing Gram-negative diplococcus morphologically resembling Neisseria meningitidis cultured from the spinal fluid. This sudden turn in events altered the therapy from sympto-

Submitted for publication Jan. 26, 1959.

From the Pediatric Service, U. S. Naval Hospital, Jacksonville, Fla.

The opinions or assertions contained in this article are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

matic and supportive to the specific use of sulfadiazine. Sodium sulfadiazine, 1 gm. diluted in 20 cc. of 5% dextrose and water was given intravenously immediately, and 2 gm. of sodium sulfadiazine in 1,000 cc. of ⅙ m lactate was begun as an intravenous drip for the next 12 hours. In addition to this, the patient was given 100 mg. of hydrocortisone intramuscularly and another 100 mg. was added to the intravenous solution. A thorough search for intimate contacts was begun. All contacts were given sulfadiazine prophylactically.

At this point, the patient was still febrile and complained of severe pain in her back and neck and retained her opisthotonic posture. No petechiae were present and the vital signs remained stable. A repeat spinal tap showed an opening pressure of 100 mm. CSF, and the fluid remained clear. No cells were present and no bacteria were noted on the smear. The spinal fluid sugar and protein were within the range of normal. Another blood culture was drawn. The following day, Sept. 9, the patient became afebrile but still had a painfully stiff neck and back. The opisthotonic posture was somewhat decreased. Examination of the organisms obtained from culture of the spinal fluid revealed that the previously reported Gram-negative diplococci were now pleomorphic, with some rod shapes present. Morphologically, the organism now closely resembled Hemophilus influenzae. At this point the possibility of a M. polymorpha infection was first suspected, and samples of the culture were sent to Dr. N. J. Schneider, Director of the Laboratory Services of the Florida State Board of Health, in Jacksonville, for a more definitive study. Chloramphenicol, 100 mg/kg/day was added to the regimen to cover the possibility of H. influenzae meningitis.

The patient remained afebrile and continued to improve daily. However, during the first seven days of her illness, she exhibited marked irritability and was a very unhappy child. Intravenous fluids were discontinued on the third hospital day, and the sulfadiazine and chloramphenicol were administered orally. On the ninth hospital day the patient was free of symptoms and all medications were discontinued. The stiffness of the neck and back were the last clinical signs to disappear. The Florida State Board of Health reported that the culture material from the patient had been identified as M. polymorpha. The details of the bacteriological identification as performed in our laboratory and by the Bacteriology Department of the Florida State Board of Health are shown in Table 1.

On the 11th hospital day a repeat spinal tap was performed; the opening pressure was 110 mm. CSF, and the fluid was clear. The cell count was one lymphocyte, and the chemistries were within normal limits. The first two spinal fluid cultures were positive for M. polymorpha and the last was sterile. Neither of the two blood cultures was positive. The micro-organism was sensitive to chlortetracycline, oxytetracycline, chloramphenicol, erythromycin, and nitrofurantoin, and resistant to penicillin and streptomycin. The patient was discharged on the 12th hospital day and has remained well for four months since leaving the hospital.

TABLE 1.—*Details of the Bacteriological Identification of Mima Polymorpha in the Case Presented*

Gram stain	Negative
Morphology	Rods, with many pleomorphic coccic forms
Motility	Negative
Culture media	Good growth on tryptone broth
Oxidase test	Negative
24-Hour urea	Negative
Dextrose	No fermentation
Xylose	No fermentation
Maltose	No fermentation
Lactose	No fermentation
Citrate	Negative
Nitrate	Negative
H_2S	Negative
Litmus milk	No change
Pigmenting agar	No pigmentation
Serotyping (specific rabbit serum) *	Positive agglutination for Mima
Precipitin typing	Not performed

* Performed at the Communicable Disease Center, Chamblee, Ga.

Comment

Bacteriology.—M. polymorpha belongs to the bacteriological tribe Mimeae. The other micro-organisms of this tribe are Herellea vaginicola and Colloides anoxydana.[7] M. polymorpha has been well classified by its culture and fermentation characteristics, chief of which is its inability to ferment any of the carbohydrate media. The positive oxidase test relied on by many laboratories for the rapid identification of N. meningitidis does not absolutely rule out the possibility of a Mima infection. Whereas most of the Mima species give a negative reaction, one variant, M. polymorpha, var. oxidans, gives a positive reaction. For a thorough review of the bacteriological identification of M. polymorpha the reader is referred to the article by Brooks and Sanders.[8]

In 1956, an ingenious method for the rapid differentiation of M. polymorpha from N. meningitidis, using serological techniques,

was reported by Cary, Lindberg, and Faber.[9] Adapting Maxted's technique for the typing of streptococci to M. polymorpha, a type specific antigen was found. Of 19 different serotypes identified, none showed a cross reaction with the Maxted extracts prepared from six strains of N. meningitidis and one each of N. sicca and N. catarrhalis. The test, which is a precipitin technique utilizing an enzymatic digestion process, lends itself readily to use by most laboratories. The authors state that with this test a type specific laboratory identification of M. polymorpha can be made in 14-18 hours from the time the spinal fluid is plated. None of the 19 serotypes identified as of 1956 was particularly associated with meningeal infections.

Clinical Aspects.—Most extensive reviews of bacterial meningitis in infants and children fail to include M. polymorpha as an etiologic agent.[10-16] It is interesting to speculate whether this may be due to its rare occurrence or whether the micro-organism is erroneously classified at times as one of the commoner bacteria it can mimic. Supporting the latter theory is the experience of Townsend et al.,[4] who sent Mima culture material from one of their patients to 13 other laboratories as a survey specimen. Not one of them identified it correctly. This ability of the micro-organism to mimic is not limited solely to its bacteriological pleomorphism but is extended to its clinical effects on the patient as well. In the one other pediatric case reported by Schuldberg[3] the patient was a 1½-year-old girl who had been ill with an upper respiratory infection for two weeks prior to the onset of her meningitis. On admission the patient had widespread petechiae and purpuric lesions over the skin and mucous membranes. A Gram-negative intracellular diplococcus indistinguishable from Neisseria meningitidis was seen on the smear taken from the petechiae. Schuldberg's patient was promptly treated with sulfadiazine and penicillin but died seven hours after admission to the hospital. The spinal fluid revealed only 50 white blood cells per cubic millimeter, 65% of which were polymorphonuclear and the culture was sterile. However, M. polymorpha was obtained in pure culture from the meninges at autopsy. Of the five remaining cases reported, all adults, four survived and one died.[2-6] The last case, one of two reported by Townsend et al.[4] was a 19-year-old airman who died with the clinical picture of the Waterhouse-Friderichsen syndrome within five hours after the onset of symptoms.

The finding of clear spinal fluid with no pleocytosis in the reported case was at first thought to be unusual; however, such findings have been described in incipient cases of meningococcal meningitis[17] and even more explicitly have been reported by Olafsson et al.[5] in another case of M. polymorpha meningitis occurring in a 63-year-old Negro patient. The spinal fluid cell count of this patient rose to only 30 white blood cells per cubic millimeter. In Schuldberg's case[3] the count rose to only 50 white blood cells per cubic millimeter even in the presence of an overwhelming infection. In other cases[2,4,6] the count has varied from 130-1,300 white blood cells per cubic millimeter. The repeatedly normal spinal fluid cell counts in the case reported cannot be explained, but the severe meningitic symptoms and the positive spinal fluid culture would seem to justify the diagnosis. The lack of pleocytosis, a feature suggested in other reported cases, was perhaps augmented by the patient being seen early in the course of the disease and the prompt institution of antimicrobial therapy. Although M. polymorpha has been cultured from normal human subjects, there is strong evidence for its pathogenicity in types of infection other than meningitis. Cases of septicemia[18] and bacterial endocarditis[19] due to M. polymorpha have been reported. It should be mentioned at this point that meningococcic meningitis can be simulated clinically by bacteria other than M. polymorpha. Other Neisseria species such as N. sicca,[20] catarrhalis,[21,24] flava,[21] flavescens,[22] and gonorrheae[23] have been reported

TABLE 2.—*Summary of the Drug Sensitivity Studies in the Seven Reported Cases of Meningitis Due to Mima Polymorpha*

Case Source	Pen.	Strep.	Sulfa.	Oxyt.	Chlort.	Tetra.	Chloram.	Eryth.	Bac.	Nitro.	Neo.	Poly B.	Novo.
DeBord[2]	No sensitivities												
Schuldberg[3]	—	—	0	+	—	0	+	0	—	0	0	0	0
Townsend et al.[4]													
Case "A"	No sensitivities												
Case "B"	+	+	0	+	+	0	+	0	+	0	0	0	0
Olafsson et al.[5]	—	—	—	+	+	+	—	+	—	+	+	+	—
Fred et al.[6]	+	+	0	+	+	0	+	0	0	0	0	0	—
Present report	—	—	0	+	+	0	+	+	0	+	0	0	0

Pen.=penicillin; Strep.=streptomycin; Sulfa.=sulfadiazine; Oxyt.=oxytetracycline; Chlort.=chlortetracycline; Tetra.=tetracycline; Chloram.=chloramphenicol; Eryth.=erythromycin; Bac.=bacitracin; Nitro.=nitrofurantoin; Neo.=neomycin; Poly B.=polymyxin B; Novo.=novobiocin.

+=Organism sensitive; —=Organism resistant; 0=Sensitivity to this drug not reported.

as the cause of meningeal infections thought to be due to N. meningitidis initially.

Sensitivity Patterns and Treatment.—What is generally known concerning the sensitivity of M. polymorpha to the antimicrobial drugs is at best somewhat confusing. Within the limits of accuracy of in vitro disc sensitivities, no two sensitivity patterns in any of the reported cases have been exactly the same (Table 2). This is no doubt due in part to the 10-year spread over which these cases have been reported and the changing antibiotic picture during that time. However, it also suggests that there are different strains with varying sensitivities and makes sensitivity studies on each new case mandatory at the present time. Of the five reported cases in which a detailed sensitivity report is included, five were sensitive to oxytetracycline, four to chloramphenicol, four to chlortetracycline, two to both penicillin and streptomycin, two to erythromycin, and two to nitrofurantoin. From these reports it would appear that oxytetracycline is the drug of choice, but in none of the reported cases has this antibiotic actually been used (Table 3). On the other hand, of the seven cases of M. polymorpha meningitis, including the present case report, five have been treated with sulfadiazine. In spite of this frequent use of sulfadiazine, little can be discerned about its efficacy since in only one case was it used alone[2] and in the other four cases in which it was employed in combination with an antibiotic, only once[6] are specific sensitivity tests for the sulfonamides reported. The general lack of reported sensitivities to the sulfonamides is due to the fact that the disc sensitivity test used by most laboratories cannot be relied upon to give accurate results when used for this group of chemotherapeutic agents. The ordinary laboratory media generally used in disc sensitivity studies contains too many sulfonamide inhibitors. A special medium excluding these inhibitors must be prepared and the sulfonamide included in the medium.[25] Since it is obligatory to use sulfadiazine in the face of a possible meningococcus infection, though it may be a masquerading M. polymorpha infection, it is suggested that it would be very informative if special sulfonamide sensitivity studies were performed in all cases of this nature. From Table 2 it can be seen that

TABLE 3.—*Summary of the Treatment Utilized in the Seven Reported Cases of Meningitis Due to Mima Polymorpha*

Case Source	Year Reported	Antimicrobial Therapy Used	Result
DeBord[2]	1948	Sulfadiazine	Survived
Schuldberg[3]	1953	Penicillin, sulfadiazine	Died
Townsend et al.[4]			
Case "A"	1954	Penicillin (before admission)	Died
Case "B"	1954	Sulfadiazine, penicillin	Survived
Olafsson et al.[5]	1958	Penicillin initially, then sulfadiazine	Survived
Fred et al.[6]	1958	Penicillin	Survived
Present case report	1959	Sulfadiazine initially then combined with chloramphenicol	Survived

there is evidence to indicate that at least one strain of M. polymorpha is sensitive to both penicillin and streptomycin.

Because meningitis due to either N. meningitidis or M. polymorpha may be a rapidly fatal disease, it is felt that sulfadiazine should be used promptly whenever a Gram-negative diplococcus is found. Until further studies are available concerning the sensitivity of M. polymorpha to the sulfonamides it is recommended that oxytetracycline or chloramphenicol be added to the therapeutic regimen if any pleomorphism is noted or if specific identification procedures such as the carbohydrate fermentation tests or the precipitin typing suggests the presence of a micro-organism other than the meningococcus. Since the physician must rely on the clinical picture and is dependent on the laboratory for the rapid identification of the offending organism in all cases of meningitis, it seems that we will continue to be misled from time to time by the mimicking abilities of M. polymorpha. But as DeBord [1] pointed out in 1939, with an etiologic agent such as M. polymorpha, we cannot be content with the initial laboratory identification of a micro-organism classified by its shape and Gram-staining characteristics alone.

Summary

A case of meningitis due to M. polymorpha occurring in a 6-year-old girl is reported. This is only the second such case in which the patient was a child. The clinical and laboratory mimicking abilities of this Gram-negative pleomorphic rod are stressed, particularly its ability to mimic a meningococcic infection. The sensitivities and therapy in each of the reported cases in the literature is summarized and discussed in an attempt to determine the treatment of choice for M. polymorpha meningitis. A paradox exists in that the apparent drug of choice, oxytetracycline, has never been used to actually treat a case of M. polymorpha meningitis. Conversely, sulfadiazine has been used in the treatment of five of the seven cases reported, and no valid sensitivity studied for this drug were performed. The need for specific laboratory identification procedures in the management of meningitis is emphasized.

U. S. Naval Hospital, Jacksonville (14), Fla.

REFERENCES

1. DeBord, G. G.: Organisms Invalidating the Diagnosis of Gonorrhea by Smear Method, J. Bact. 38:119-121 (July) 1939.

2. DeBord, G. G.: Mima Polymorpha in Meningitis, J. Bact. 55:764-765 (May) 1948.

3. Schuldberg, I. I.: Clinical and Pathological Simulation of Meningococcic Meningitis: Report of Case with Necropsy, Am. J. Clin. Path. 23: 1024-1027 (Oct.) 1953.

4. Townsend, F. M.; Hersey, D. F., and Wilson, F. W.: Mima Polymorpha as a Causative Agent in Waterhouse-Friderichsen Syndrome, U. S. Armed Forces M. J. 5:673-679 (May) 1954.

5. Olafsson, M.; Lee, Y. C., and Abernathy, T. J.: Mima Polymorpha Meningitis, New England J. Med. 258:465-470 (March 6) 1958.

6. Fred, H. L.; Allen, T. D.; Hassel, H. L., and Holtzman, C. F.: Meningitis Due to Mima Polymorpha, A. M. A. Arch. Int. Med. 102:204-206 (Aug.) 1958.

7. Breed, R. S.; Murray, E. G. D., and Hitchens, A. P.: Bergey's Manual of Determinative Bacteriology, Ed. 6, Baltimore, The Williams & Wilkins Company, 1948.

8. Brooks, B. E., and Sanders, A. C.: "Unidentified" Gram Negative Rods and the Tribe Mimeae, U. S. Armed Forces M. J., 5:667-672 (May) 1954.

9. Cary, S. G.; Lindberg, R. B., and Faber, J. E., Jr.: Typing of Mima Polymorpha by the Precipitin Technique, J. Bact. 72:728-729 (Dec.) 1956.

10. Alexander, H. E.: Advances in the Treatment of Bacterial Meningitis, Advances Pediat. 5:13-52 (Jan.) 1952.

11. Lepper, M. H.; Blatt, N. H.; Wehrle, P. F., and Spies, H. W.: Treatment of Bacterial Meningitis of Unusual Etiology and Purulent Meningitis of Unknown Origin, A. M. A. Am. J. Dis. Child. 85:295-302 (March) 1953.

12. Smith, E.: Purulent Meningitis in Infants and Children: A Review of 409 Cases, J. Pediat. 45:425-436 (Oct.) 1954.

13. Severy, W. L.: Meningitis: A Review of the Year's Cases from an Active Children's Hospital Service, California Med. 82:436-439 (June) 1955.

14. Smith, M. H. D.: Acute Bacterial Meningitis, Pediatrics 17:258-277 (Feb.) 1956.

15. Carson, M. J. and Koch, R.: Management of Bacterial Meningitis in Children, Pediat. Clin. North America, pp. 377-398 (May) 1956.

16. Cavanaugh, J. J. A., and Kline, A. H.: Review of Bacterial Meningitis in Children at the Harriet Lane Home, Johns Hopkins Hospital, unpublished data.

17. Daniels, W. B.; Solomon, S., and Jaquette, W. A. Jr.: Meningococcal Infection in Soldiers, J. A. M. A. 123:1-9 (Sept. 4) 1943.

18. Faust, J., and Hood, M.: Fulminating Septicemia Caused by Mima Polymorpha: Report of Case, Am. J. Clin. Path. 19:1143-1145 (Dec.) 1949.

19. Pike, R. M.; Schulze, M. L., and McCullough, M.: Isolation of Mima Polymorpha from Patient with Subacute Bacterial Endocarditis, Am. J. Clin. Path. 21:1094-1096 (Nov.) 1951.

20. Bansmer, C., and Brem, J.: Acute Meningitis Caused by Neisseria Sicca, New England J. Med. 238:596-597 (April 22) 1948.

21. Brainerd, H., and Bradley, E.: Treatment of Bacterial Meningitis with Penicillin and Sulfonamides, California Med. 66:57-62, (Feb.) 1947.

22. Branham, S. E.: A New Meningococcus Organism, (Neisseria flavescens) Pub. Health Rep. 45:845-849 (Aug.) 1930.

23. Branham, S. E.; Mitchell, R. H., and Brainin, W.: Gonococcic Meningitis, J. A. M. A. 110:1804-1806 (May 28) 1938.

24. Corfield, W. F.: Multiple Attacks of Cerebrospinal Fever, Lancet 1:402-403 (March 31) 1945.

25. Daeschner, C. W.; Clark, J. L.; Yow, E. M., and Townsend, E.: Comparative Evaluation of the Sulfonamides, J. Pediat. 50:531-551 (May) 1957.

Congenital Absence of Most of the Colon

Anomaly Associated with Imperforate Anus, Syndactylism, and Polydactylism

ZAFAR HUSAIN ZAIDI, M.B., B.S. (Lucknow), Ottawa, Canada

Congenital anomalies of the large bowel are not very rare. The commonest congenital lesions of the large bowel are anomalies of rotation and peritoneum attachment, megacolon and microcolon, atresia and stenosis. Many such cases have been recorded and discussed fully in the literature. The case presented here illustrates the extremely rare abnormality of absence of most of the colon.

Report of Case

History.—A 3-day-old female infant was admitted to Ottawa General Hospital, on Aug. 18, 1958, because of persistent vomiting since birth. The mother had threatened abortion about the eighth week of pregnancy; the baby was delivered at full term, weighing 6 lb. 2 oz. (2,790 gm.). The parents were French Canadians without consanguinity.

Physical Examination.—Restless baby of average build, temperature 95.8 F (axillary), pulse 140/minute and respiration 24/minute. Left hand was normal; the right hand showed syndactylism between index, middle, and ring fingers. The left foot revealed syndactylism between first and second toes. The right foot exhibited polydactylism, having six toes, and syndactylism between first and second toes and then between third, fourth, fifth, and sixth toes (Fig. 1).

The abdomen was distended and tympanitic but peristalsis was not visible, and free fluid could not be elicited in the peritoneal cavity. Bowel sounds could be heard, particularly over the lower abdomen. The anus was imperforate and was represented by a tract ⅛×1 in. running backward and upward, behind the vagina. Other systems were apparently normal.

Skiagrams of the abdomen were taken, which showed marked distention of abdomen filled with loops of intestine, without apparent distention of the "sigmoid colon." There was suggestion of low intestinal obstruction. The length of the "uncanalized segment" was not demonstrable (Fig. 2).

Laparotomy.—In view of these findings, an immediate laparotomy was performed. The intestines were much distended. The stomach, small bowel, appendix, and cecum appeared normal. Only 1½ in. of the proximal ascending colon was present and ended blindly (Fig. 3). The rest of the ascending, transverse, and descending colon, the sigmoid and rectum were completely absent, and no remnant could be found. The blind end of the bowel was exteriorized and the abdomen closed. The baby

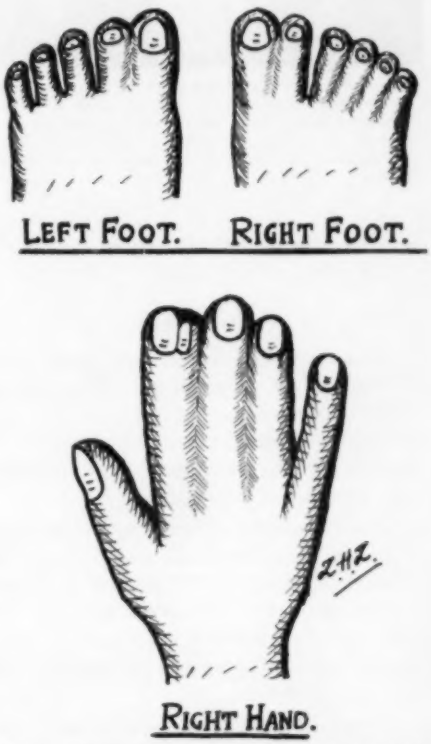


Fig. 1.—Left foot showing syndactylism; right foot showing syndactylism and polydactylism, and right hand showing syndactylism and a half-supernumerary nail.

Submitted for publication Jan. 15, 1959.

Chief Resident in Paediatrics, Ottawa General Hospital, and Department of Paediatrics, University of Ottawa.

Fig. 2.—Straight anteroposterior skiagram of the abdomen in inverted position, with a rubber catheter placed in the tract in anal region, showing marked distention of abdomen filled with loops of intestine. "Uncanalized segment" is not demonstrable.

stood the operation well but later deteriorated and died 14 hours after admission.

Comment

Complete absence of the large bowel from the end of the proximal part of ascending colon to the anal canal represents failure of proper development of the whole of the hindgut and the distal part of the postarterial segment of the midgut.

The association of syndactylism or polydactylism with intestinal anomalies is not uncommon. Out of 198 patients with congenital anal and rectal anomalies who also had other congenital anomalies, which Gross [1] recorded, one had syndactylism and five polydactylism.

Douglas [2] reported the case of a 32-year-old patient who had congenital absence of the part of the colon derived from the midgut and stenosis at the junction of small

Fig. 3.—As seen on laparotomy, the intestines are distended, only 1½ in. of proximal colon is present and ends blindly. The tip of the appendix is held by forceps.

and large bowels, causing acute intestinal obstruction. This patient also had carcinoma in the distal colon. Haxton [3] published a case report of a 2-day-old infant with congenital absence of continuity between small and large bowels. Heckel and Apfelbach [4] published a review of 30 cases of atresia of the intestine, which included many in whom a segment of the bowel was absent; they failed to clarify how often he found absence of a portion of the colon. In a photograph, by Potter,[5] showing atresia of the duodenum, the colon apparently terminates at about the hepatic flexure. Potter [6] has also seen termination of the colon immediately above the cecum.

Summary

A case of an infant is presented and briefly discussed who had congenital complete absence of colon from the first inches of the ascending colon to the anal canal, in addition to imperforate anus, syndactylism, and polydactylism.

I wish to thank Dr. D. J. Conway, Professor of Paediatrics, for his kind help and Dr. W. E. Nelson and Dr. J. B. Arey, of Philadelphia, and Dr. E. L. Potter, of Chicago, for their helpful information. I also express my thanks to Dr. F. H. Côté and Dr. H. Bourque for permission to publish this case.

43 Bruyère St. (2).

REFERENCES

1. Gross, R. E.: The Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1953, p. 355-356.

2. Douglas, K.: Absence of Part of Colon, Associated with Carcinoma of Colon, Brit. J. Surg. 41:373, 1954.

3. Haxton, H.: Congenital Absence of Continuity Between Small and Large Intestine with Abnormal Blood Supply of the Proximal Colon, Brit. J. Surg. 32:540, 1945.

4. Heckel, N. J., and Apfelbach, C. W.: Congenital Atresia of the Colon, Am. J. Dis. Child. 34:1050, 1927.

5. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, The Year Book Publishers, Inc., 1952, p. 304.

6. Potter, E. L.: Personal communication to the author.

Abstracts from Current Literature

American Journal of Pathology, Ann Arbor, Mich.
Abstracted by Jay Bernstein, M.D.

35, No. 1 (Jan.-Feb.) 1959

* Subacute Glomerulonephritis. Jacob Churg and Edith Grishman.—p. 25.
* The Structural Basis of Proteinuria in Man: Electron Microscopic Studies of Renal Biopsy Specimens from Patients with Lipid Nephrosis, Amyloidosis, and Subacute and Chronic Glomerulonephritis. David Spiro.—p. 47.
Botryomycosis. Donald J. Winslow.—p. 153.
The Effect of Cortisone and Antibiotic Agents on Experimental Pulmonary Aspergillosis. Herschel Sidransky and Lorraine Friedman.—p. 169.

Subacute Glomerulonephritis.—The anatomic changes in the kidney of subacute glomerulonephritis were studied in autopsy material by light microscopy, using thin (0.5μ) tissue sections stained with Schiff, silver methenamine, and dialyzed iron procedures. Alterations interpreted as occurring in the disputed glomerular intercapillary space or mesangium were regarded as a direct continuation of pathologic changes previously described by the same authors in acute glomerulonephritis. In the acute stage edema, inflammatory cells, and an increased number of mononuclear cells were seen in the mesangium; the deposition of fine, Schiff-positive fibers in this space marked the beginning of the subacute stage. Hyaline material progressively accumulated, and the space was converted into a fibrohyaline mass or scar. Proliferation of the parietal epithelial cells of Bowman's capsule, with splitting and duplication of the basement membrane of Bowman's capsule, led to the development of epithelial and fibrous crescents. Changes in the capillary walls included both irregular attenuation of the basement membrane, with accumulation of hyaline masses apparently in the capillary lumen, and thickening of the capillary wall. The latter, which was the commoner, was due in part to splitting of the basement membrane, possibly by extension of exudate from the intercapillary space, to form a narrow pericapillary space. Thickening and splitting were also associated with subendothelial deposition of hyaline, imparting a "wire-loop" appearance to the glomerular loops. Finally, thickening occurred as the result of a subepithelial layer of hyalin, containing Schiff-positive, silver-positive spikes; the last changes correspond to the "membranous" glomerulonephritis described by others. Some endothelial cell enlargement occurred, and in the nephrotic syndrome the endothelial cytoplasm was swollen and vacuolated.

The anatomic lesions were mixed and overlapped, but intercapillary alterations predominated in the cases with the lowest average age at the time of death. Membranous transformation was seen in cases with the highest average age and of the longest clinical duration. Of 10 cases with a fully developed nephrotic syndrome, 5 had intercapillary and "wire-loop" lesions and 5 had membranous transformation. The latter was most pronounced in cases of the longest duration, and particularly so when the patients had had the nephrotic syndrome before but not at the time of their deaths. Membranous transformation was also associated in three instances with renal vein thrombosis. The authors therefore suggest that membranous transformation is the consequence rather than the cause of the nephrotic syndrome.

The Structural Basis of Proteinuria in Man: Electron Microscopic Studies of Renal Biopsy Specimens from Patients with Lipid Nephrosis, Amyloidosis, and Subacute and Chronic Glomerulonephritis.—In cases of lipid nephrosis, amyloidosis, and subacute and chronic glomerulonephritis with proteinuria, electron microscopy showed that interruptions in the basement membrane are a consistant structural alteration. Transformation of the foot processes of the glomerular epithelial cells into broad cytoplasmic sheets was also found. In cases of lipid nephrosis, the breaks in the basement membranes were as much as 1,000 A. in extent, and at these interruptions the epithelial and endothelial cells were in direct contact. The amyloid was deposited subendothelially, and it progressively penetrated and replaced the basement membranes; the amyloid could be characterized as a loose meshwork of thin filaments. The author points out that aside from the obvious explanation that the epithelial

* These articles are abstracted in this issue.

transformation is an attempt to plug the leaky basement membrane, the basement membrane simultaneously undergoes irregular thickening and the change in the epithelial foot processes may reflect an increased production of the former. At any rate, the defects in the basement membrane and the loosely fibrillary amyloid seem to be responsible for the increased diffusion of protein from the glomerulus.

American Review of Tuberculosis and Pulmonary Diseases, New York

Abstracted by Edwin L. Kendig, Jr., M.D.

79, No. 1 (Jan.) 1959

Experiments on the Antituberculous Activity of Alpha-Ethyl-Thioisonicotinamide. Noël Rist, Francoise Grumbach, and David Libermann.—p. 1.

Observations on the Antituberculous Effectiveness of Alpha-Ethyl-Thioisonicotinamide in Tuberculosis in Humans. G. Brouet, J. Marche, N. Rist, J. Chevallier, and G. LeMeur.—p. 6.

The Natural History of Tuberculosis in the Human Body: 1. The Demonstrable Primary Pulmonary Infiltrate.—p. 19.

* Late Discharge of Tubercle Bacilli in Primary Tuberculosis. Edith M. Lincoln and Amparo C. Adiao.—p. 31.

Infectivity and Immunogenicity of Mycobacterium X in Mice. Emanuel Suter and Anne K. Strain.—p. 47.

The Lymphatics Which Drain the Potential Space Between the Visceral and the Parietal Pleura. Hugh E. Burke.—p. 52.

The Antituberculous Activity of Kanamycin in Vitro and in the Experimental Animal (Guinea Pig). W. Steenken Jr., Vincent Montalbine, and J. R. Thurston.—p. 66.

Progress Toward the Standardization of BCG Vaccine. René J. Dubos.—p. 80.

An Urban Focus of Histoplasmin Sensitivity. D. L. Aronson and P. Q. Edwards.—p. 83.

Determination of Growth Rates of Atypical Strains and of Other Mycobacteria as a Means of Estimating Optimal Growth Periods for Comparative Biochemical Studies. M. Gastambide Odier and D. W. Smith.—p. 94.

Acquired Resistance and Isoniazid Medication. K. Bartmann et al.—p. 97.

Method of Obtaining BCG. S. R. Rosenthal.—p. 105.

Treatment Failures. S. Jacobs.—p. 105.

79, No. 2 (Feb.) 1959

Tissue Culture Studies on Resistance in Tuberculosis: II. Monocytes from Normal and Immunized Guinea Pigs Infected with Virulent Human Tubercle Bacilli. Morgan Berthrong and Mary Alice Hamilton.—p. 221.

* Giant Lymph Node Hyperplasia of the Mediastinum: Case Report with a Review of the Literature. Kiyoshi Inada, Keizo Kawai, Tatsuki Katsumura, and Akinori Nakano.—p. 232.

Mediastinal Tuberculosis Manifested by Pericarditis, Osteochondritis, and Broncho-Esophageal Fistula. Robert E. Shope and Robert G. Petersdorf.—p. 238.

Circulating Levels of the "Plasma Factor" Responsible for in Vitro Leukocyte Cytolysis During Sensitization of Guinea Pigs with M. Tuberculosis. B. W. Janicki.—p. 244.

Experimental Reinfection in Arrested Guinea Pig Tuberculosis and Its Behavior Under Isoniazid Therapy. F. Bastarrachea et al.—p. 246.

Serum Enzymes in Pulmonary Tuberculosis: Glutamic Oxalacetic Transaminase and Glutamic Pyruvic Transaminase. J. L. Herring et al.—p. 251.

* A Comparison of Spirometric and Douglas Bag Measurements of Maximal Breathing Capacity. D. G. Stuart and A. A. Cohen.—p. 253.

79, No. 3 (March) 1959

Purified Protein Derivatives (PPD) and Other Antigens Prepared from Atypical Acid-Fast Bacilli and Nocardia Asteroides. Lewis F. Affronti.—p. 284.

Some Biologic Properties of Mycobacteria Following the Extraction of Lipids: The Power to Initiate Acquired Resistance. Armand Frappier, Vincent Portelance, and Jacques St.-Pierre.—p. 296.

* Prednisone in the Treatment of Tuberculous Pleural Effusions. Samuel S. Paley, John P. Mihaly, Edward L. Mais, S. Aubrey Gittens, and Belardino Lupini.—p. 307.

A Study of the Nature of Arterial Oxygen Lack Using an Improved Rapid Method of Measuring Oxygen Tension. William F. Miller, Brian J. Sproule, and Ivan E. Cushing.—p. 315.

Sonic Fragility of Leukocytes from Guinea Pigs Vaccinated with BCG. Robert A. Patnode and Paul C. Hudgins.—p. 323.

Investigation of the Influence of Antimicrobial Drugs on the Allergic Reactions to Reinfection Tuberculosis in Rabbits. Yukio Kitazawa and Shigeo Ohta.—p. 329.

The Influence of 3,3',5-Triiodo-L-Thyronine on the Survival Time of Mice with Tuberculosis and Pneumococcosis. J. E. Nutter, C. L. Gemmill, and Q. N. Myrvik.—p. 339.

A Critical Analysis of the Accuracy of a Chemical and Biologic Method of Determining Serum-Free Isoniazid. Stephen J. Berte, Howard C. Leifheit, Hal J. Dewlett, and Elon B. Tucker.—p. 344.

The Tolerability of Calcium Benzoyl-PAS and Calcium PAS: A Double Blind Study. K. Jeker, H. Lauener, J. Regli, and T. Friedrich.—p. 351.

Mucormycosis of the Lung: A Case Without Significant Predisposing Factor. Herman W. Blankenberg and Dirk Verhoeff.—p. 357.

Nonreactive Tuberculosis. Mario Montes and Charles Phillips.—p. 362.

Genetic Considerations of the Mechanisms Involved in PAS-Resistant Tubercle Bacilli. M. Tsukamura et al.—p. 371.

Preliminary Report on Vaccines Prepared from Gamma-Irradiated Mycobacterium Tuberculosis and Brucella Suis. C. M. Carpenter et al.—p. 374.
A Pilot Study of the Tuberculin Test for Case Finding in a General Hospital. E. W. Custer.—p. 378.
Failure of Polyoxyethelene Ether (Triton WR 1339) to Protect Against Tuberculin Shock in Guinea Pigs. R. A. Patnode and P. C. Hudgins.—p. 382.

79, No. 4 (April) 1959

* The Pathology of 1957 (Asian) Influenza. Donald D. Mark.—p. 440.
Respiratory Function Tests: Normal Values at Median Altitudes and the Prediction of Normal Results. H. I. Goldman and Margaret R. Becklake.—p. 457.
Microscopic Enumeration of Mycobacteria in Pulmonary Lesions of Tuberculous Mice: Effect of Prior BCG Vaccination. G. Conge, E. Collin, F. M. Levy, and R. J. Dubos.—p. 484.
Morphology of Healing Processes in Chemotherapy: Translation of a Soviet Review. V. I. Puzik and O. A. Uvarova.—p. 497.
Serum Protein Electrophoretic Pattern and Middlebrook-Dubos Titer in Tuberculous Children Following BCG Vaccination. C. Choremis et al.—p. 522.
Bronchograms Under Hypnosis. K. K. Kaufman.—p. 525.
Quantitative Aspects of Neutral Red Reactions of Typical and "Atypical" Mycobacteria. L. G. Wayne.—p. 526.
The Use of Enzymes to Aid Filtration of Oropharyngeal Washes Through Membrane Filter. H. Wolochow et al.—p. 541.
Histoplasmin Sensitivity in Alaskan Natives. G. W. Comstock.—p. 542.

Late Discharge of Tubercle Bacilli in Primary Tuberculosis.—The fact that tubercle bacilli may be discharged a long time after the onset of primary tuberculosis without any roentgenographic or clinical change in the patient seems to be established. However, the significance of such a finding is questionable.

In a review of the experience in the Chest Clinic of the Children's Medical Service of Bellevue Hospital, the authors found that tubercle bacilli were cultured from gastric or bronchial fluid 6 months to more than 25 years after the initial diagnosis of primary tuberculosis in 44 patients. No significant roentgenographic changes accompanied the late excretion of tubercle bacilli. Twenty-seven patients had endobronchial disease proved by endoscopy, and an additional eight had roentgenographic or bronchographic findings suggestive of previous endobronchial involvement. Foci of tuberculosis draining into the upper respiratory tract, usually in tonsils and adenoids, were found in 11 of the 44 patients.

The authors suggest that it would seem reasonable to treat or retreat with antimicrobial therapy all children in whom tubercle bacilli reappear on culture within two years of a known primary focus, in the hope of eradicating the lesion producing tubercle bacilli before it becomes a closed necrotic focus. Persons showing tubercle bacilli on culture long after a known primary infection or with roentgenographic evidence suggesting arrested primary tuberculosis with or without previous endobronchial involvement should be subjected to careful study by bronchoscopy, bronchography when necessary, and repeated bacteriologic examinations. In the occasional cases in which roentgenograms are normal, otolaryngologic examination should be undertaken. It is advised that all such cases be carefully studied prior to decision regarding chemotherapy or surgery.

Giant Lymph Node Hyperplasia of the Mediastinum: Case Report with a Review of the Literature.—Malignant lymphoma, manifested as lymphosarcoma or Hodgkin's disease, is the commonest neoplasm among mediastinal tumors. On the other hand, benign tumors of lymphoid origin, either inflammatory or neoplastic, are exceedingly rare. The authors report a case of localized lymph node hyperplasia, which on microscopic section revealed reactive lymphoid hyperplasia resembling a thymoma.

A Comparison of Spirometric and Douglas Bag Measurements of Maximal Breathing Capacity.—The Douglas bag and standard spirometers are widely used to record maximal breathing capacity. Although Shephard has questioned the reliability of results obtained by the former method, the authors found the mean Douglas bag measurement to be 6% higher than the mean spirometric measurement. They conclude, however, that the additional advantages of the standard spirometer outweigh this slight discrepancy.

Prednisone in the Treatment of Tuberculous Pleural Effusions.—Accepting that tuberculous pleurisy with effusion is a particularly hyperergic manifestation of tissue sensitivity to tuberculin, it follows that especial benefits could logically be expected from the antiallergic action of corticotropin and the corticosteroids. Moreover, their anti-inflammatory properties should prevent the formation of organized pleural exudates, a particularly distressing sequel of long-standing effusions.

Twenty-six patients (adults) were treated with dihydrostreptomycin, isoniazid, and prednisone, which were started immediately after an initial thoracentesis. The steroid was used in gradually decreasing doses down to a maintenance level, and was continued for four weeks—and, in one case, six weeks. One dose of corticotropin was given at the termination of treatment. Intrapleural instillations were not used. All patients showed a remarkable symptomatic response in 24 to 48 hours.

With this regimen the fluid was found to clear in three to six weeks, with a median of five weeks. The average hospital stay ranged from 3 to 12 weeks, with a median of 8 weeks. This was in marked contrast to previous experience on the same hospital service where residual effusion persisted up to six months in about 25% of the cases, and, in a smaller percentage, persisted much longer, with ventilatory crippling secondary to fibrous organization of the residual exudates.

The amount of fluid present originally apparently had no bearing on the rapidity or totality of the response. Only one patient required a repeat thoracentesis. In another, a coexistent pulmonary lesion cleared in four months. Of the 26 patients in this series 12 showed roentgenographic clearing to the point of a normal film, and the remaining 14 showed minimal degrees of basal pleural thickening as a permanent stigma. Disabling fibrothorax was not observed. On the basis of these results, the authors believe that tuberculous pleural effusions constitute a definite added indication for the use of steroid therapy.

The Pathology of 1957 (Asian) Influenza.—Since the great pandemic of 1918, the pathology of influenza has been exhaustively studied. The isolation in 1933 by Smith, Andrewes, and Laidlaw of a human influenza virus cleared away all doubt as to the essential character of the disease and provided the necessary tool for assessing the train of tissue changes in infected persons.

The author studied 17 deaths which occurred during the 1957 epidemic period. Evidence of influenzal infection was established in six patients by viral isolation from the lung, and in four patients by antibody studies. The lungs of all of the patients showed a characteristic necrotizing tracheobronchitis with foci of squamous metaplasia in the mucosa which is considered a distinctive feature of influenzal viral infection. Two patients exhibited isolated tracheobronchitis, without complicating pneumonia. The importance of Staphylococcus aureus as a predominant superinfecting organism in fatal cases was indicated. It has been postulated that staphylococci may produce the specific train of bronchopulmonary changes encountered in this and other studies, but there is no unassailable evidence for it.

Bulletin of The Johns Hopkins Hospital, Baltimore

Abstracted by Thomas K. Oliver, Jr., M.D.

104, No. 1 (Jan.) 1959

* Kartagener's Triad: A Family Study. George W. Gorham and John G. Meraelis Jr.—p. 11.
Clinical Manifestations of Hemoglobin C Disorders. Ernest W. Smith and Julius R. Krevans.—p. 17.

Kartagener's Triad: A Family Study.—Since 1933, when Kartagener described the syndrome of bronchiectasis, situs inversus, and sinusitis which bears his name, occasional cases occurring in siblings have been reported. To date, family studies have not been performed. The authors observed the triad in two young adult siblings, both of whom had had symptoms since early childhood. The family, through four generations, was studied and the literature since 1950 reviewed with respect to familial incidence. In this review, the authors discovered six cases in which there was a familial incidence, all of whom involved only siblings. This was in keeping with the finding of the family study in the authors' cases; and all four generations were otherwise free of symptoms suggested from the triad. The authors conclude that Kartagener's triad may have a high familial incidence but appears only in one generation, which suggests that during embryonic development there is some environmental factor present which is responsible for the appearance of the triad rather than a genetic factor.

Canadian Medical Association Journal, Toronto

Abstracted by H. M. Keith, M.D.

80, No. 1 (Jan. 1) 1959

* Aminophylline Poisoning in Children. H. L. Bacal, K. Linegar, R. L. Denton, and R. Gourdeau.—p. 6.
The Dangerous Hypodermoclysis in Infancy. S. Israels and K. Wylie.—p. 31.
The Application of the Human Blood Groups to Blood Transfusion. B. P. L. Moore.—p. 51.

80, No. 2 (Jan. 15) 1959

* Trifluoperazine Dihydrochloride: An Effective Tranquilizing Agent for Behavioural Abnormalities in Defective Children. L. J. LeVann.—p. 123.
Dementia Infantilis. R. Gibson.—p. 114.
Acute Neonatal Neutropenia in Siblings. A. E. Buckwold and H. E. Emson.—p. 116.

80, No. 3 (Feb. 1) 1959

Fetal Masculinization with Progesterone Therapy. D. A. Hillman.—p. 200.
A Plea for Vitamin C Fortified Milk. H. Medovy.—p. 213.

80, No. 4 (Feb. 15) 1959

* The Family Doctor and the Handicapped Child and Young Adult. D. Paterson.—p. 286.

80, No. 5 (March 1) 1959

* A Clinical and Statistical Study in Cerebral Palsy Rehabilitation. G. Gingras, V. Susset, R. R. Lemieux, J. M. Chevrier, G. Huot, R. Voyer, G. Skuhrovsky, and C. Quirion. p. 342.
* Primary Peptic Ulcer in Children: Report of 14 Cases and Review of Literature. A. W. Alvi and A. G. Rogers. (Résumé).—p. 352.

80, No. 6 (March 15) 1959

* Influence of Steroid Therapy on the Nephrotic Syndrome in Children. R. M. Ehrlich, C. P. Rance, and R. J. Slater.—p. 430.
* Analysis of Intrauterine Malformations of the Vertebral Column Induced by Oxygen Deficiency. K. H. Degenhardt and E. Knoche.—p. 441.
Idiopathic Hypercalcaemia of Infancy. J. C. Haworth.—p. 452.
Intravenous Therapy in Infants and Children. W. A. Cochrane.—p. 471.

Aminophylline Poisoning in Children.—Aminophylline is used frequently in the management of bronchial asthma. Poisoning can occur from its therapeutic use. The authors present 10 cases of aminophylline poisoning from the record of the Children's Hospital in Montreal. Most of the children were young, under 5 years. The youngest was a 16-month-old girl who was given 2 grains of aminophylline every four hours for four doses and showed signs of toxicity in 24 hours. The oldest was a 10-year-old boy who was given 7½ grains of aminophylline in a single intravenous dose. Within 15 minutes he had signs of toxic effect but recovered well within three days.

The authors discuss the pharmacology of the xanthines briefly and note that the clinical manifestations of aminophylline overdosage may be (1) central nervous system stimulation, with unusual restlessness and irritability, (2) prolonged increase in gastric secretion, manifested by nausea, vomiting or hematemesis, (3) increased urine output, (4) cardiovascular collapse, or even death. The authors recommend the following dosage: (*a*) oral suspension tablets, 5 mg. per kilogram of body weight; the dose may be repeated every eight hours, but not oftener than every six hours, (*b*) rectal suppository or retention enema, 7 mg. per kilogram of body weight; this may be repeated every eight hours but not oftener than every six hours and is to be restricted to cases where oral administration is not practicable. These doses have been found adequate for treatment of asthmatic children and have not caused any undesirable side-effects.

Treatment of the toxic phase is purely symptomatic, aimed at sedation, support of respiration and circulation, and the prompt prevention or correction of dehydration.

Trifluoperazine Dihydrochloride: An Effective Tranquillizing Agent for Behavioural Abnormalities in Defective Children.—During the past decade the development of tranquilizing drugs has been of great help in the treatment of psychiatric patients. The author reports the effect of trifluoperazine dihydrochloride in children in an institution for mental defectives. These children presented problems of biting, hitting out, self-inflicted injuries, feeding difficulties, and hyperkinesis. He studied a group of 33 patients who did not respond to the better known ataractic drugs. In this group of patients all other sedative and tranquilizing drugs were stopped and a 12-hourly dosage of trifluoperazine was begun, using 1 mg. twice daily for all patients under 60 lb. in weight and 2 mg. twice daily for patients weighing between 61 and 100 lb. This last dose was increased somewhat for patients over 100 lb. if they showed no reduction in their antisocial behavior or their overactivity. The dosages given ranged from 2 to 3 mg. daily to 15 mg. daily.

Immediate improvement was noted in less than 48 hours in all of the 33 patients tested and dramatic reduction of abnormal activity was recorded. The therapy was carried out over an eight-week period. Daily urine specimens showed no renal disturbance, and weekly blood

analyses carried out on each patient showed no abnormalities over the eight-week period. The only abnormal reaction noted was in one juvenile schizophrenic patient who developed slight tremor in both hands.. These signs disappeared within 12 hours of withdrawal of trifluoperazine. The author states that this drug makes considerably easier the care of hyperactive mentally defective children.

The Family Doctor and the Handicapped Child and Young Adult.—The medical profession, from its training and outlook, should direct the care and treatment of children handicapped by disease, abnormal development, or any disability. The author states that teamwork is essential, and that complete diagnostic services must be available. The physician must help in family and school planning, as well as in carrying out specific treatment, and give advice regarding future employment. He recommends that a registry of handicapped children be established, that questions regarding the child's condition at birth be included in the birth certificate, that traveling clinics be established, and that the physician be prominent in discussions as to the child's education and training.

A Clinical and Statistical Study in Cerebral Palsy Rehabilitation.—The authors screened 250 cerebral patients but observed 137 in detail. They covered medical, psychological, speech, occupational therapy, and social service aspects. Many patients availed themselves of the services of two, three, or more hospitals, as well as chiropractors and "quacks," and it is pointed out that lack of medically organized facilities may be responsible for this.

Postnatal causes for cerebral palsy were noted in 31% of cases, contrary to previous reports of 10%. Fifty-six per cent had speech defects, twenty-one per cent epilepsy, and sixty-six per cent were mentally deficient. Mental deficiency was found to be a major hindrance for speech learning.

Psychological and psychiatric findings are discussed, e. g., reactions of parents, reactions of the children and their families. Acceptance of the cerebral palsied child was almost always good in rural families, and large families seemed more able to cope with the problem. It is suggested that the best way to modify the attitudes of parents is to bring their ambivalent feelings into the open through group discussion.

Primary Peptic Ulcer in Children: Report of 14 Cases and Review of Literature.—Available literature on the subject of peptic ulcers in children has been reviewed. The case records of 10 boys and 4 girls between the ages of 10 and 16 years admitted during 1948 to 1957 to St. Boniface Hospital were selected and reviewed. Twelve patients had duodenal ulcer. The incidence corresponds well with the reported increased frequency in males and predominance of duodenal over gastric ulcer.

The symptoms seemed to follow the adult pattern, and bleeding from the gastrointestinal tract seemed to be common. However, five patients had no bleeding but had radiological evidence of peptic ulcer. The importance of roentgenological examination in children with abdominal complaints of obscure nature has been clearly defined. Radiological criteria for diagnosis of peptic ulcer in children have been discussed.

Children usually respond satisfactorily to a conventional medical regimen.

Influence of Steroid Therapy on the Nephrotic Syndrome in Children.—One hundred thirty-four patients with the nephrotic syndrome were studied between 1951 and 1956. Twenty-three of these were followed for a period of 48 months. Of these 23 patients, 14 were completely well at the end of the four years and 5 were clinically well, with some persistent proteinuria. The authors calculate the survival rate then to be 81% at four years. This figure compares favorably with Riley's 75% survival following steroid therapy.

In the presteroid period, 1946 to 1950, authors noted a 61% survival rate for four years and feel that the use of steroids has increased this appreciably. The authors then point out that it cannot be said that a higher percentage of children are ultimately cured of the disease since relapses have occurred after four years of apparently normal health.

Analysis of Intrauterine Malformations of the Vertebral Column Induced by Oxygen Deficiency.—The authors report experimental work in rabbits with the aim of producing malformations in embryos at an early stage of development by subjecting them to a single exposure of four hours of oxygen deficiency. It was found possible to produce disturbances in the early anlage of the vertebral column between the 8th and 10th days of embryonic development in these rabbits. Sensitivity to alterations was greatest on the ninth day of

pregnancy. The authors obtained 112 embryos and fetuses from 15 pregnancies by interrupting the gestations. These fetuses and embryos regularly showed developmental anomalies of the vertebral column. The histological character of these anomalies is described and there are photomicrographs to illustrate this. The defects found corresponded to hereditary defects occasionally seen in mice.

Journal of Clinical Endocrinology and Metabolism, Springfield, Ill.

Abstracted by Judson J. Van Wyk, M.D.

18, No. 9 (Sept.) 1958

The Delta Cell of the Human Adenohypophysis: Its Response to Acute and Chronic Illness. C. Ezrin, H. E. Swanson, J. G. Humphrey, J. W. Dawson, and W. D. Wilson.—p. 917.

Adrenocortical Carcinoma in Man: The Effect of Amphenone on Individual Ketosteroids. T. F. Gallagher.—p. 937.

Comparison of the Metabolic Effects of Different Thyroid Preparations. L. H. Kyle, J. J. Canary, R. J. Meyer, and F. P. Pac.—p. 950.

° Renal Regulation of Phosphorus Excretion. Ralph Goldman and Samuel H. Bassett.—p. 981.

Iodine Metabolism of Endemic Goiter on the Aland Islands (Finland). B.-A. Lamberg, P. Wahlberg, O. Wegelius, G. Helström, and P. I. Forsius.—p. 991.

° Gonadal Dysgenesis: Case Report of a 6-Year-Old Boy with a Fallopian Tube and an Undifferentiated Gonad. J. T. Bradbury and R. G. Bunge.—p. 1006.

A Review of "Auto-Immunization" in Hashimoto's Disease. C. A. Owen Jr.—p. 1015.

Thyroid Function of Euthyroid Patients During and After Treatment with Triiodothyronine. C. Rich.—p. 1024.

Concerning the Reversibility of Osteoporosis. M. Moldawer.—p. 1028.

The Effect of Food on the 3-Hour Thyroidal Uptake of I^{131} in Human Subjects. D. J. Turell, A. S. Littell, and R. P. Levy.—p. 1029.

18, No. 10 (Oct.) 1958

The Thermogenic Effect and Metabolic Fate of Etiocholanolone in Man. A Kappas, L. Helman, D. K. Fukushima, and T. F. Gallagher.—p. 1043.

Studies on Biologic Characterization of Human Gonadotropins: II. Comparison of HPG and GCG. A. Albert and S. Kelly.—p. 1067.

The Secretion and Disposition of Cortisol During Pregnancy. M. Cohen, M. Stiefel, W. J. Reddy, and J. C. Laidlaw.—p. 1076.

Depression of Serum and Urinary Citric Acid Levels by 17-OH-CS. D. H. Henneman and P. H. Henneman.—p. 1093.

Effect of Fluorine on Thyroidal Iodine Metabolism in Hyperthyroidism. P. M. Galleti and G. Joyet.—p. 1102.

Effects of Hypo- and Hyperthyroidism on Filterability of Serum Magnesium. C. R. Kleeman, F. H. Epstein, D. McKay, and E. Taborsky.—p. 1111.

Collaborative Assays of Two Urinary Preparations of Human Pituitary Gonadotropin. A. Albert, R. Borth, E. Diczfalusy, J. A. Loraine, B. Lunenfeld, J. W. McArthur, and E. Rosenberg.—p. 1117.

Androgenic Pattern of Serum Lipids and Lipoproteins in Response to CGH in Male Hypogonadism. R. P. Howard and R. H. Furman.—p. 1123.

° Prolonged Turnover Rate of Hydrocortisone in the Newborn Infant. A. M. Bongiovanni, W. R. Eberlein, M. Westphal, and T. Boggs.—p. 1127.

Osteoporosis in Hyperadrenocorticism. J. E. Howard.—p. 1131.

Renal Concentrating Ability in Thyrotoxicosis. F. H. Epstein and M. J. Rivera.—p. 1135.

Complications During Administration of Methylestrenolone. J. C. Seelen.—p. 1137.

18, No. 11 (Nov.) 1958

Role of Adrenal Cortex in Normal Adaptation to Dietary Sodium Deprivation. J. Crabbe, W. J. Reddy, E. J. Ross, and G. W. Thorn.—p. 1147.

Significance of Secretion of Aldosterone During Dietary Sodium Deprivation in Normal Subjects. J. Crabbe, E. J. Ross, and G. W. Thorn.—p. 1159.

Divergence in Mg, Na and K Excretion During Stimulation of Endogenous Aldosterone Production. T. R. Miller, W. W. Faloon, and C. W. Lloyd.—p. 1178.

Urinary Excretion of ICSH and FSH Activity During the Normal Menstrual Cycle. J. W. McArthur, J. Worcester, and F. M. Ingersoll.—p. 1186.

Urinary Excretion of ICSH and FSH Activity by Women with Diseases of the Reproductive System. J. W. McArthur, F. M. Ingersoll, and J. Worcester.—p. 1202.

Quantitative Determination of Progesterone and Pregnanediol in Human Plasma. I. F. Sommerville and G. N. Deshpande.—p. 1223.

Inhibition of the Sodium-Retaining Influence of Aldosterone by Progesterone. R. L. Landau and K. Lugibihl.—p. 1237.

Radiocalcium Studies of Bone Formation Rate in Human Metabolic Bone Disease. R. P. Heaney and G. D. Whedon.—p. 1246.

Simplified Method for Routine Measurement of Urinary Estriol. W. R. Eberlein, A. M. Bongiovanni, and C. M. Francis.—p. 1274.

° Influence of Tranquilizing Drugs on Results of Thyroid Function Studies. S. Newman and V. J. Fish.—p. 1296.

18, No. 12 (Dec.) 1958

Testicular and Adrenal Response to ACTH and HCG in Man. L. L. Hibbitt, W. R. Starnes, and S. R. Hill Jr.—p. 1315.

Clinical Effect of Human Pituitary FSH. C. A. Gemzell, E. Diczfalusy and G. Tillinger.—p. 1333.

* Familial True Hermaphrodism in Pre- and Postpuberal Genetic Females: Hormonal and Morphologic Studies. G. W. Clayton, J. D. Smith, and H. S. Rosenberg.—p. 1349.

* Seminiferous Tubule Dysgenesis (Klinefelter's Syndrome) in Identical Twins. D. A. Holub, M. M. Grumbach, and J. W. Jailer.—p. 1359.

Cytology of Human Urinary Sediment: Diagnostic Value of the Non-Nucleated Cell. H. Castellanos and S. H. Sturgis.—p. 1369.

Virilizing Adrenal Adenoma with Increased Urinary Estrogens and 17 KS. Isolation of Steroids from the Tumor. M. Keller, A. Hauser, and A. Walser.—p. 1384.

Fractionated Plasma Protein Values in Subacute Thyroiditis. P. G. Skillern and L. A. Lewis.—p. 1407.

Simplified Water Loading Test in Hypoadrenocorticism and Hypothyroidism. A. M. Moses, J. L. Gabrilove, and L. J. Soffer.—p. 1413.

Effect of Insulin on Serum Lipoproteins of Diabetic Patients. E. H. Strisower, R. O. Weed, J. W. Gofman, B. Strisower, and O. F. deLalla.—p. 1418.

Determination of Sex Chromatin in the Polymorphonuclear Neutrophils of Enriched Smears. J. Procopio-Valle, W. A. Chagas, and A. de Freitas.—p. 1432.

19, No. 1 (Jan.)1959

* Effect on Maternal Thyroid Function on Fetal Thyroid Function and Development. E. A. Carr Jr., W. H. Beierwaltes, G. Raman, V. N. Dodson, J. Tanton, J. S. Betts, and R. A. Stambaugh.—p. 1.

TSH Content of the Human Hypophysis. J. L. Bakke and N. L. Lawrence.—p. 35.

Effect of Desiccated Thyroid in Lymphocytic Thyroiditis. W. M. McConahey, L. B. Woolner, B. M. Black, and F. R. Keating Jr.—p. 45.

Struma Lymphomatosa and Related Thyroidal Disorders. L. B. Woolner, W. M. McConahey, and O. H. Beahrs.—p. 53.

Further Studies on Use of In Vitro RBC Uptake of 1-Triiodothyronine ^{131}I as a Diagnostic Test of Thyroid Function. M. W. Hamolsky, A. Golodetz, and A. S. Freedberg.—p. 103.

* Occurrence of Thyroid Nodules in Children Following I^{131} Therapy for Hyperthyroidism. G. E. Sheline, S. Lindsay, and H. G. Bell.—p. 127.

* Exophthalmic Goiter in Children. A. B. Hayles, R. L. J. Kennedy, O. H. Beahrs, and L. B. Woolner.—p. 138.

Renal Regulation of Phosphorus Excretion.—Normal adult males on a metabolic balance regimen were studied from the standpoint of serum phosphorus, filtered phosphorus, tubular reabsorption of phosphorus, and urinary phosphorus. During periods of phosphorus loading the serum level of phosphorus rose and the urinary excretion increased. Most of the initial rise in urinary phosphorus was due to increased glomerular filtrate rather than to an abrupt change in tubular reabsorption. Changes in the tubular reabsorption of phosphorus occurred irregularly and only after 48 hours of phosphorus loading. These findings indicate that the parathyroid hormone appears to regulate renal function in response to sustained rather than transient variations in the dietary phosphorus load.

Gonadal Dysgenesis: Case Report of a 6-Year-Old Boy with a Fallopian Tube and an Undifferentiated Gonad.—The authors describe the internal genitalia and gonadal structures in a 6-year-old child who externally exhibited hypospadius and cryptorchidism. The chromosomal pattern, as determined by buccal smear, was negative. The right gonad was located in the inguinal region and was attached to a spermatic cord and epididymis. Internally there was a well-developed uterus and left Fallopian tube. The left gonad consisted of a pale, white, fibrous structure in the normal position of an ovary.

The right gonad, histologically, resembled a prepubertal testis, except that the germinal elements exhibited varying degrees of pleomorphism and undifferentiation. An occasional tubule contained a peculiar spherical body, which the authors believe is characteristic of gonadal dysgenesis. The left gonad consisted of whorls of connective tissue and closing masses of pleomorphic germ cells. The general appearance was that of an embryonic polar-differentiated gonad.

Comment.—This case furnishes an additional example that prenatal testicular integrity is required for the normal differentiation of male genital ducts and that the inductor action of each testis is exerted unilaterally. These findings are in line with the classical experiments of Jost, but fail to shed any light on the cause of the defective gonadal development.

Prolonged Turnover Rate of Hydrocortisone in the Newborn Infant.—Hydrocortisone was administered to a group of infants, children, and adults, and the biologic half-life of the administered steroid measured by determining the levels of phenylhydrazine reacting substances in the plasma at one and three hours. On the first day of life the disposition of hydrocortisone was considerably slower than in all other age groups. The mean in this group

was 977 minutes as contrasted with a mean of 96 minutes in the age group 1-12 years. The half-life became shorter between the third and ninth days of life but was still longer than in older children. The disappearance curve of tetrahydro E on the first day of life was identical with that observed in older children. It would therefore appear that the slow disappearance of hydrocortisone in the newborn may be due to a relative deficiency in the enzymes responsible for the reduction of ring A rather than a relative inability to conjugate the reduced steroid with glucuronic acid. It is suggested that the high levels of estrogen from the mothers may be responsible for the observed results.

Influence of Tranquilizing Drugs on Results of Thyroid Function Studies.—A study was made of the effect of various tranquilizing drugs on various parameters of thyroid function. The 24-hour uptake of I^{131} by the thyroid gland, the PBI level, and serum cholesterol level were determined in both euthyroid and hyperthyroid patients who were receiving promazine, meprobamate, hydroxyzine, or reserpine. None of these drugs produced any demonstrable change in the objective tests of thyroid function as compared with the results of tests carried out during a control period. The clinical manifestations of thyrotoxicosis were frequently ameliorated during treatment with these ataraxic drugs.

Comment.—Children respond slowly to specific antithyroid drugs and reserpine has proved to be a valuable adjunct in the early period of therapy before the antithyroid drugs take hold. Ataraxic agents were initially used, since they have been shown to act on subcortical areas of the nervous system and many thyroidologists believe that Graves' disease is basically a disease of the hypothalamus. The dramatic action of tranquilizing drugs on thyroid storm (Canary, J. J.; Schaaf, M.; Duffy, B. J., and Kyle, L. H.: Effects of Oral and Intramuscular Administration of Reserpine in Thyrotoxicosis, *New England J. Med.* 257:435 [Sept. 5] 1957) suggests a specific role of these agents on thyroid function. All studies to date, however, have failed to demonstrate any objective changes in thyroid function.

Familial True Hermaphrodism in Pre- and Postpuberal Genetic Females: Hormonal and Morphologic Studies.—Studies of gonadal histology and steroid excretion were carried out in two brothers who were born with hypospadias without cryptorchidism. The older brother developed progressive breast enlargement from the age of 13 years. By the age of 16 he had developed fairly good secondary male sexual characteristics, but his proportions were eunuchoid. His urine contained low normal quantities of 17-ketosteroids, increased amounts of prednandiol and estrogen, and normal levels of gonadotrophic hormones. His chromatin pattern was positive, as was that of his brother. Exploration of his scrotal contents revealed small testes with the typical picture of seminiferous tubular dysgenesis (Klinefelter's syndrome) and a small attached body, which proved to be ovarian tissue containing primordial and atretic follicles. Following removal of the ovarian tissue the urinary excretion of pregnandiol and estrogen fell sharply.

The 7-year-old prepubescent brother had no gynecomastia and on physical examination was found to be normal, except for the presence of repaired hypospadias and somewhat small gonads. On biopsy these gonads likewise were found to contain both testicular and ovarian tissue. The histological morphology of the testes in the younger boy was essentially normal.

Seminiferous Tubule Dysgenesis (Klinefelter's Syndrome) in Identical Twins.—Two 17-year-old identical twins presented with the classical clinical features of seminiferous tubule dysgenesis (Klinefelter's syndrome). Both boys had a positive chromatin pattern, and the usual histological features of this syndrome were demonstrated by testicular biopsies. It was ascertained that the boys were single ovum twins by blood group typing, dermatoglyphics, and by means of reciprocal homografts.

Comment.—During the past several years there has been renewed interest in the syndrome of seminiferous tubular dysgenesis since it has been demonstrated that these individuals have a positive (female) chromatin pattern. The syndrome has been found to be far commoner than previously suspected, especially among children with mental deficiency and behavior disturbances. The frequent occurrence of this disorder within families provides evidence that the disorder is genetically determined rather than acquired by injury to the fertilized ovum or fertilization of an overripe ovum. The family reported by Clayton is of particular importance since the findings in his patients clearly link the syndrome of seminiferous tubular dysgenesis to true hermaphrodism, an association which previously has been only inferred. The recent finding that patients with Klinefelter's syndrome possess 47 chromosomes with

XXY sex chromatin suggests that either the ovum contained two X chromosomes or that a normal ovum was fertilized by a sperm cell carrying both an X and a Y chromosome.

Effect of Maternal Thyroid Function on Fetal Thyroid Function and Development.—Seventeen mothers of cretins were examined 2 months to 24 years after the birth of their last cretinous child. All but one of the mothers was euthyroid. The mother who was hypothyroid had borne two previous cretins, as had one euthyroid mother in the group. Each of these mothers who had previously given birth to two previous cretins became pregnant during the course of the present study. Each of these mothers was treated with massive doses of thyroid hormone during her pregnancy (20-30 grains of desiccated thyroid per day!) in an attempt to protect the fetuses against possible hypothyroidism in utero. This treatment was given because previous studies have indicated that there is incomplete transport of maternal thyroid hormone across the placental barrier. One of these babies was normal at birth, although there was temporary suppression of his thyroid function postnatally. The other infant was born prematurely, but had normal protein-bound iodine at birth and no evidence of prenatal hypothyroidism. The authors judged that this child was a cretin, however, because the PBI curve progressively fell postnatally and because he had a subnormal uptake of I^{131}, which failed to rise after TSH. For this reason he was started on thyroid substitution therapy at the age of 9 days. At the age of six months this child was developing normally and gave no evidence of mental retardation.

Comment.—Athyrotic cretinism typically occurs sporadically without familial or genetic predisposition. No documentation is provided in the present paper to exclude the possibility of a genetically determined enzymatic defect of the thyroid hormones in those families where more than one cretin had been born. It is difficult to evaluate the evidence upon which the authors based their diagnosis of cretinism in the child of the mother who had received massive thyroid therapy during her pregnancy. It is conceivable that this child's thyroid had undergone temporary atrophy due to the massive thyroid medication administered to the mother.

Occurrence of Thyroid Nodules in Children Following I^{131} Therapy for Hyperthyroidism.—Between May, 1945, and July, 1953, 213 patients with toxic diffuse goiter were treated definitively with I^{131} at the University of California Hospital, San Francisco. In this group were five patients less than 10 years of age at the time of therapy and 13 patients who were between the ages of 10 and 20 years. Two of the five patients who were less than 10 years of age at the time that treatment was given developed nodules in their thyroid glands after 8 and 10 years respectively. One of the 13 patients between the ages of 10 and 20 years developed thyroid nodules 5½ years after therapy. In the 195 patients over the age of 20 years who had been treated with radioactive iodine, only two nodules were discovered in the follow-up period. The initial doses of radioactive iodine given to the children ranged between 1.8 mc. and 3.6 mc. All of these patients were subjected to thyroidectomy after the appearance of nodules, and in most instances the histological picture was that of a follicular adenoma. One nodule which had perforated the capsule was classified as an invasive adenoma or a low-grade follicular carcinoma. These studies suggest that the child's thyroid is more sensitive to the neoplastic effects of radiation than is that of the adult.

Comment.—Previous studies have indicated that thyroid carcinoma can result from external radiation of the thyroid gland in infancy, and the present studies serve as a further warning that radiation to the neck should be minimized in infants and children. Children with thyrotoxicosis can usually be satisfactorily treated with propylthiouracil or potassium perchlorate. In some clinics, subtotal thyroidectomy is the procedure of choice, and in other clinics surgery is reserved for those patients who fail to cooperate in medical management or who are unduly sensitive to antithyroid drugs. It should be pointed out that the amounts of radioactive iodine administered to these children were several hundred times larger than the tracer doses used in diagnostic studies. So far there has been no documented instances of adverse effects resulting from the judicious use of tracer dosages of I^{131} in the diagnosis of thyroid disorders.

Exophthalmic Goiter in Children.—A total of 253 children, less than 15 years of age, with exophthalmic goiter have been seen at the Mayo Clinic during the 48-year period 1908 through 1955. The sex ration was 6:1 in favor of girls. Exophthalmos was generally less severe than that occurring in adults, but tended to persist after all other signs of thyrotoxicosis had disappeared. Diabetes mellitus was observed more frequently in this group of children

than would be expected as a chance occurrence. Subtotal thyroidectomy has proved to be a safe method of treatment, and there have been no hospital deaths since 1933. Recurrence of hyperthyroidism has not been eliminated by more extensive resection of the thyroid gland. Of the 196 patients, 28 treated by subtotal thyroidectomy are known to have had recurrences of hyperthyroidism of such severity as to require further definitive treatment. Seven additional patients have had mild recurrences. Most of these patients have had second thyroidectomies and a few have been operated on more than twice. Three patients had recurrences more than 25 years after their initial treatment. Myxedema occurred in a high percentage of the patients treated by extensive subtotal resection of the gland. Hypoparathyroidism, keloid formation in the operative scars, and injury to the recurrent laryngeal nerves occurred but rarely in this group of patients.

Journal of Pediatrics, St. Louis

Abstracted by Demetrius G. Traggis, M.D.

54, No. 1 (Jan.) 1959

The Antibiotic Prophylaxis of Bacterial Complications of Measles. S. Karelitz and H. D. Isenberg.—p. 1.

° Intrauterine Bacterial Infection of the Newborn Infant. Kurt Benirschke and Stewart H. Clifford.—p. 11.

Anhidrotic Ectodermal Dysplasia: Use of the Silver Nitrate Plate to Detect Anhidrosis. L. B. Glicklich and I. M. Rosenthal.—p. 19.

Activity of Serum Aldolase and Lactic Dehydrogenase in Patients Affected with Duchenne Muscular Dystrophy and in Their Immediate Relatives. H. C. Soltan and M. C. Blanchaer.—p. 27.

Effect of Socioeconomic Status on the Vitamin Content of Milk. A. D. Deodhar and C. V. Ramakrishnan.—p. 34.

Neonatal Omphalitis and Pyelonephritis. W. E. Delaney.—p. 36.

The Myxedema Reflex in Infants and Children with Hypothyroidism. C. Y. Bowers, D. L. Gordon, and A. Segaloff.—p. 46.

Comparison of Intramuscular Iron-Dextran and Oral Ferrous Sulfate in the Treatment of Iron-Deficiency Anemia. W. L. Yu, K. Manonmani, and J. Watson.—p. 50.

Rheumatic Pneumonitis: Pathologic Features. R. F. Scott, W. A. Thomas, and J. M. Kissane.—p. 60.

Advantages of Floating Lipiodol as a Further Test for Voiding Efficiency. M. S. Roberts and J. K. Lattimer.—p. 68.

The Relationship Between "Mixed Dominance" and Reading Disabilities. R. L. Spitzer, R. Rabkin, and Y. Kramer.—p. 76.

Pediatric Empyema: A Second Look at Its Incidence and Importance. W. B. Kiesewetter, J. R. Rusnock, and B. R. Girdany.—p. 81.

Congenital Interruption of the Aortic Arch. P. G. Quie, R. Novick, P. Adams, R. C. Anderson, and R. L. Varco.—p. 87.

Anomalous Course of Left Pulmonary Artery: A Cause of Obstructive Emphysema in Infants. F. E. Sherman.—p. 93.

Congenital Choanal Atresia. M. D. Weinstock.—p. 99.

Varicella Gangrenosa. A. M. Crocker and J. N. Middelkamp.—p. 104.

Juvenile Xanthogranuloma with Ocular Involvement. R. Gharib, E. C. Burke, and L. A. Brunsting.—p. 109.

Foreign Bodies in the Vagina of Children. J. P. Ambuel.—p. 113.

The Children's Medical Center.—p. 116.

Leukemia and Ionizing Radiation. R. J. Blattner.—p. 124.

54, No. 2 (Feb.) 1959

Cardiovascular Surgery in a Children's Hospital. R. Ash, J. Johnson, C. E. Koop, S. Friedman, and W. Rashkind.—p. 133.

Plethora in the Newborn Infant Associated with Cyanosis and Convulsions. J. L. Wood.—p. 143.

Bone Marrow Studies in the Newborn Infant at High Altitudes.—p. 152.

Intestinal Polyposis with Oral Pigmentation. L. W. Falkinburg and M. N. Kay.—p. 162.

A Comparison of Meprospan (Sustained Action Meprobamate Capsule) with Other Tranquilizing and Relaxing Agents in Children. H. W. Baird.—p. 170.

The Effects of Kwashiorkor on the Development of the Bones of the Knee. P. R. M. Jones and R. F. A. Dean.—p. 176.

Hypophosphatemic Rickets Due to Glomerular and Tubular Renal Insufficiency. G. A. Fromm, J. F. Roca, E. Fideleff, E. Hecker, and E. Lynch.—p. 185.

Handling Parental Pressure for T and A.—R. A. Furman.—p. 195.

Interscorer Agreement for the Graham Behavior Test for Neonates. J. F. Rosenblith and L. P. Lipsitt.—p. 200.

Fulminating Purpura with Gangrene of Lower Extremity Necessitating Amputation. R. D. Turin, S. Mandel, and L. Hornstein.—p. 206.

° Phenylketonuria: An Unusual Case. Stanley A. Leonard and Frederick L. McGuire.—p. 210.

The Children's Medical Center.—p. 215.

Protein-Calorie Malnutrition in Tropical Preschool Children. D. B. Jelliffe.—p. 227.

Rubella During Pregnancy. R. J. Blattner.—p. 257.

Intrauterine Bacterial Infection of the Newborn Infant.—The authors report on a practical method for diagnosing intrauterine infection shortly after birth. They point out that the presence of prolonged rupture of placental membranes per se does not necessarily result in an infected fetus. Likewise the presence of intact membranes does not necessarily prevent intrauterine infection. In this method a 3 cm. piece of umbilical cord is cut out of the mid-portion of the umbilical cord in suspected cases. This section is placed in the test tube with approximately 10 cc. of 10% formalin and brought to a boil over a Bunsen burner. This enhances the ability to section the cord and renders staining more permanent. The fixed segment is then placed in cold water, and a frozen section is prepared at 8μ-12μ with a conventional frozen section microtome, using CO_2. The section is then strained by any method with which the pathologist is familiar. Fetal infection is indicated by the microscopic finding of inflammation of the wall of the umbilical vein. The first sign is the margination of leukocytes at the intima. Then comes infiltration of the vein wall by polymorphonuclear leukocytes. At a later stage, the inflammatory cells migrate into Wharton's jelly, and surround the vein and arteries. Bacteria may sometimes be identified in the small folds on the surface of the cord.

The authors found that in 1,300 consecutive deliveries in which this test was done the incidence of vasculitis was 10%. Of this 10%, chorioamnionitis was found in 12.7%. The authors feel that the mere finding of the vasculitis does not indicate antibacterial treatment, but that it helps to determine in the presence of other symptoms such as respiratory distress, jaundice, etc., the necessity for starting antibacterial therapy. The authors also point out that in certain viral infections of the fetus, inflammation of the umbilical cord and chorion does not occur.

Phenylketonuria: An Unusual Case.—The authors report a case of phenylketonuria in a patient of borderline mentality. Their patient was an 8-year-old girl who had been diagnosed at the age of 6 years. She had no neurologic abnormalities or skin complications. She was a little short for her age. Her electroencephalogram was moderately abnormal. Serum phenylalanine level was 36.5 mg/100 ml. (normal approximately 0.8-2.0 mg/100 ml.). Several test procedures gave her an I. Q. of about 70, and she was found to have a talent for rote memory. Environmental influences had produced several problems. Special education classes plus a more stable home life produced a great deal of improvement. She was not put on a diet. The authors discussed the chemical abnormality and the usual features. They reviewed the literature concerning mental retardation in this disease, referring to several cases in which intelligence was borderline. They feel that with the discovery of more cases of this sort the spectrum of this disease will prove to be quite broad as far as mental retardation is concerned.

Monatsschrift für Kinderheilkunde, Berlin

Abstracted by Hans Hartenstein, M.D.

106, No. 7 (July) 1958

Follow-up Studies of 356 Premature Infants. S. Molnár and B. Andrásofszky.—p. 317.
Weight Gain in Premature Infants. Elisabeth and Rolf Degen.—p. 320.
Quantitative Tests for Maturity of Prematures. G. A. von Harnack and H. Oster.—p. 324.
Signs of Maturity in Premature and Full-Term Infants. Hans Kaendler.—p. 328.
Neurology of Prematures. G. Wohlmuth and R. Pertorini.—p. 334.
Well Water Containing Nitrates as a Cause of Methemoglobinemia in Infants. Hildegard Creutzburg.—p. 336.
Hemophilia in Childhood Due to Blocking Substances. Herbert Bruester and Hans-Guenther Staemmler.—p. 338.
Peculiarities in the Structure of Sex-Differentiating Leukocytic Nuclei in Pfaundler-Hurler's Disease. Hans-Rudolf Wiedemann.—p. 341.
Review Article: Tuberculosis. A. Wunderwald.—p. 345.

106, No. 8 (Aug.) 1958

Clinical Diagnosis of Cerebral Abscess in Infancy. Klaus Dietel.—p. 353.
Results of the Treatment of Tuberculous Meningitis with Oral Neoteben. Josef Gehrt.—p. 357.
Diagnosis and Treatment of Paroxysmal Tachycardia in Infancy and Childhood. Wilhelm Heck and Joachim Stoermer.—p. 361.
Complications of Pneumonia in Infancy in the Course of Changing Treatments. N. Urban and H. Guthoff.—p. 367.
"Non-Sclerosing Ileitis" and Its Relationship to "Umbilical Colic." Wolfgang Duckert and Heinrich Stein.—p. 371.
Observations Regarding the Hemato-Morphological Diagnosis of Nuclear Sex. H. Romatowski, M. Tolkadorf, and H. R. Wiedemann.—p. 380.
Idiopathic Infantile Hypercalcemia. Gy. Koranyi.—p. 381.
Review Article: The Digestive Tract. E. Hoen.—p. 387.

Clinical Diagnosis of Cerebral Abscess in Infancy.—Brain abscess is a rare occurrence in infancy. Mortality is high, and speedy diagnosis imperative. Spinal fluid findings compatible with inflammatory change, especially if the causative organism can be found, are extremely helpful. Localizing intracranial symptoms and signs should be looked for. Pneumoencephalogram will show space-occupying signs and electroencephalogram slow waves.

Abstracts from the Soviet Literature

A selection of abstracts drawn from the current issue of Abstracts of Soviet Medicine, *a quarterly journal published by the Excerpta Medica Foundation (New York Academy of Medicine Building, 2 E. 103d St., New York 29), with the aid of a grant from the U. S. Public Health Service*

Cardiovascular System

Idiopathic myocarditis in young children Idiopaticheskii miokardit u detei rannego vozrasta. SEMENOVA E. I. *Uch. Zap. II Mosk. Med. Inst.* 1957, 3 (17-28)

A description of 14 cases of idiopathic myocarditis with fatal issue, occurring in children 2 months to 3 years of age, is given. The aetiology is unknown; the majority of authorities presume that it is only a symptom of a general constitutional affection. In 10 children the onset was acute and severe, with dyspnoea, restlessness, cold extremities, unconsciousness, and cold sweat. One child developed convulsions at the onset of the disease, and another started with abdominal pain. There was a gradual development in the lungs of pneumonia, and in the heart of dullness of sounds, embryocardia, gallop rhythm and systolic murmur. Arterial pressure was low. ECG showed involvement of the myocardium. Leucocytosis in the blood was registered without shift to the left, while the ESR ranged from 3-17 mm. in an hour. Morbid-anatomical investigation showed a marked enlargement of all cardiac cavities and flaccid cardiac muscle; microscopical investigation revealed a diffuse of focal infiltration by lymphohistiocytes, chiefly of the subendocardiac and subepicardiac layers, and albuminous dystrophy of muscle fibres, which showed thinning and fibrillolysis. Spleen and liver were enlarged in all children, and kidneys and meninges congested; there were no thrombi or emboli in the heart ventricles. Treatment was without effect.

Clinico-anotomical features in pericarditis of various aetiology in children Klinikoanatomicheskie paralleli perikarditov raznoi etiologii u detei. ROSHCHINA G. A. *Uch. Zap. II Mosk. Med. Inst.* 1957, 3 (29-34)

Pericarditis was detected in 85 children who died from various diseases, but was clinically diagnosed in only 45. In 61 cases the aetiology was rheumatic, in 22 it developed as a result of sepsis, in one case the cause was chronic nephritis in the uraemic stage, and in one case chronic pneumonia. The main symptoms were sharp pain in the cardiac region and a pericardial friction rub, which is the most remarkable feature, but it is inconstant and sometimes lasts only a matter of hours. The combination of pericarditis in rheumatism with simultaneous implication of the aortic valves was found in 25 patients and at postmortem examinations on 42 children.

Gastrointestinal System

Effect of lipocaine on the course of acute and chronic dysentery in children Vliyanie lipokaina na techenie ostroi i khronicheskii dizenterii u detei. BELENKOVA M. A. *Vopr. Okhr. Mater. i Dets.* 1957, 3 (27-30)

The effect of lopocaine (lipotropic substance from pancreas) was studied in 90 children up to 5 years of age, who suffered from acute, protracted and chronic dysentery. All children were admitted to the hospital in serious or moderately serious condition with symptoms of dystrophy; in the majority there were noted enlargement of liver and doughiness of cellular tissue. Various complications and associated illnesses were observed in many. Lipocaine was prescribed at the rate of half a tablet 3 times daily during 10 days. Its high therapeutic efficiency was noted: the children's state of health improved, appetite reappeared, the stools became normal, weight increased, the size of the liver became normal, and complications were rapidly cured. The recovery of patients with chronic dysentery was speeded up considerably. At the basis of the preparation's therapeutic activity lies reduction of fatty infiltration and improvement of the liver function.

The relation between the resistance of the dysentery group of bacteria to antibiotics and the clinical course of the illness Svyaz ustoichivosti bakterii dizenteriinoi gruppy k antibiotikam s klinicheskim techeniem zabolevaniya. NEVEROVA E. I. *Vopr. Okhr. Mater. i Dets.* 1957, 3 (30-33)

Determination was made of sensitivity to synthomycin (chloramphenicol) and streptomycin displayed by 675 strains of dysenteric bacteria isolated from patients with dysentery. Meat-peptone broth was used as the culture medium. All strains were found sensitive to streptomycin, and 55.1% of the strains to synthomycin. Parallel observations were made of 133 children with various forms of dysentery, who received synthomycin in age-scaled doses. The percentage of coincidences between the sensitivity of isolated strains to synthomycin and timely bacterial purification reached 71.4. In treatment with streptomycin the percentage of coincidences was still higher.

Complex treatment of chronic dysentery in children aged up to 3 years, living in children's homes O kompleksnom lechenii khronicheskoi dizenterii u detei v vozraste do 3 let v usloviyakh doma rebenka. LAVRISHCHEVA N. A. and CHERNOVA A. I. *Vopr. Okhr. Mater. i Dets.* 1957, 3 (37-40)

Treatment was given to 75 children suffering from chronic dysentery (therapy is indicated) with undoubted positive effect. Bacteria-carrying was stopped in 34 out of 47 children in whom dysentery was confirmed bacteriologically; rapid normalization of the stool was recorded. The treatment was less effective in the group of children with dysentery unconfirmed bacteriologically. Proper nutrition and regimen have great importance, in addition to combined therapy with antibiotics and 'immunogen' (not traced. Ed. A. S. M.).

The significance of the thymol-veronal test in children suffering from chronic dysentery Znachenie timol-veronalovoi proby u detei, bolnykh zatyazhnoi (khronicheskoi) dizenteriei. SUKACHEVA G. I. *Pediat. Akush. i Ginek.* 1957, 3 (19-21)

Two hundred two tests were undertaken on 76 children. The results varied between 0 and 4 units. Before treatment the test was positive in the majority of cases (above 7 units). The actual figure obtained then depended on the duration and form of the disease and on the efficacy of treatment. The values remained high in complicated and relapsing cases.

Nervous System

Conditioned reflex activity of young children on diets in conformity with their age requirements Uslovnoreflektornaya deyatelnost detei rannego vozrasta na fone pitaniya sootvetstvenno vozrastnym potrebnostyam. RATMANOVA O. N. *Pediatriya* 1957, 7 (68-70)

Conditioned reflex activity of 18 children (1.5-3 years) in a home was investigated. The diet was in conformity with age requirements: 4 g. protein, 4 g. fat, 13-14 g. carbohydrates per kg. of weight. In addition the children were given 50 mg. of ascorbic acid, and 1 mg. of vitamin B_1; cod-liver oil and vitamins A and D were given when indicated. The weight of the children was average for their age. In the investigation of conditioned reflexes 2 methods were used—vascular and motor-alimentary. The following characteristics were found: (1) The vascular component is manifest mostly in vasodilatation. (2) The appearance of spontaneous reactions—motor and vascular—in the period between the activity of conditioned stimuli; this is explained by the insufficiency of the processes of internal inhibition. It can be assumed that any external stimulus, even when inconsiderable, provokes a strengthening of the excitation focus, arising in connection with the formation of a conditioned reflex. (3) Excitation processes, feebly pronounced vascular reflex reactions, and also their distorted character under the effect of cold, were prevalent. This led to the problem of the need to train the vascular system in children (hardening of the constitution), beginning at a very early age.

Vascular reactions in dysentery in young children Sosudistye reaktsii pri dizenterii u detei rannego vozrasta. ALYABEVA M. M. *Pediat. Akush. i Ginek.* 1957, 3 (13-16)

Sixteen children suffering from acute dysentery and 34 healthy children were under observation. The results of plethysmography of 12 patients pointed to weakening of cortical function with increased excitability of vasomotor centres. The reactions of inhibitory nature were obtained in 4 children with dysentery of moderate severity.

Functional state of cerebral cortex in dysentery in young children Funktsionalnoe sostoyanie kory golovnogo mozga pri dizenterii u detei rannego vozrasta. TRETYAK M. A. *Pediat. Akush. i Ginek.* 1957, 3 (21-24)

Forty-seven children with acute, 18 with chronic dysentery and 16 healthy children were under observation. In the case of the sick children the conditioned reflexes were late to develop,

easily effaced and had a long latent period. The equilibrium of excitatory-inhibitory processes in the cortex was disturbed and increased subcortical excitability was noted. Restitution of normal cortical function occurred later than clinical cure.

Eye, Ear, Nose, and Throat

Objective examination of vestiges of hearing in deafmute children Obektivnoe issledovanie ostatkov slukha u glukhonemykh detei. Sokolov E. N. and Paramonova N. P. From the book: *Ostatochnyi slukh u tugoukhikh i glukhonemykh detei (Moscow)* 1957 (36-50)

While the state of the auditory analysor is best appreciated through the direct responses of the auditory system to sound, it is however difficult to register such responses. Conditioned responses require prior development and further reinforcement. Orientation reactions are very convenient, though they fade rapidly. In order to obtain exact data, the authors recorded simultaneously electroencephalograms and the dermogalvanic vascular responses of 32 deaf 10- to 15-year-old individuals. In addition, vibrograms were taken of a number of children. The method of registering both the orientation reaction and the conditioned motor responses to sound makes it possible to get a fairly complete picture of the function of the auditory analysor. The use of sound stimuli, which act as signals, reveals the subthreshold range of sensitivity to sound. In comparing the audiograms with the vibrograms one can determine various types of relationship of sensitivity to sound and to vibration in deafmutes. This enables one to differentiate between true vestiges of hearing capacity and diffuse sensitivity to vibrations.

Aims and problems of otiatric observation in schools and institutions for hard-of-hearing and deafmute children of preschool age Tseli i zadachi otiatricheskogo nablyudeniya v shkolakh i doshkolnykh uchrezhdeniyakh dlya glukhonemykh, i tugoukhikh detei. Shcheglova F. E. From the book: *Ostatochnyi slukh u tugoukhikh i glukhonemykh detei (Moscow)* 1957 (116-122)

The author outlines the work of the medical specialist in otiatrics in schools and institutions for deaf and hard-of-hearing children of preschool age. She stresses that otolaryngologists who work in these organizations must study more thoroughly the problem of deafness and hardness-of-hearing, especially the questions of classification and diagnosis of these disorders, as well as of standardization of terminology. It would be practical to develop ear specialists with training in pediatrics and to organize in the Public Health system research and methodology centres where studies could be conducted on problems of deafness in children.

Nutrition, Deficiency Diseases

Role of certain vegetables in mineral metabolism of children Rol nekotorykh ovoshchei v mineralnom obmene detei. Shitskova A P., Gnoevaya V. L., Kalinina K. A. and Myshevskaya M. I. Food Hygiene Department, Erisman Sanitary Scientific Research Institute, Moscow *Vopr. Pit.* 1958, 17/1 (54-58)

Data are set forth on investigations into the metabolism of calcium, phosphorus, magnesium and nitrogen in children who received a food ration with predominance of groats and a ration with partial replacement of groats by carrot or sauerkraut. The caloric value of the rations amounted to 2,200 calories on the average. The metabolism was studied in four 9- to 10-year-old boys. During the period of the metabolism study (10-11 days), the children received four sorts of diet. It was found that inclusion of carrot and sauerkraut in the child nutrition ration with corresponding reduction in the quantity of groats somewhat increases the balance of nitrogen, calcium and phosphorus. The highest balance of nitrogen and mineral substances (calcium, phosphorus, magnesium) was observed in children who had received a ration with carrot.

Application of mazun in the mixed feeding of infants K voprosu o primenenii matsoni pri smeshannom vskarmlivanii rebenka. Geri E. I. and Papava V. V. *Pediatriya* 1957, 7 (30-33)

Fifty-six infants aged from 2 weeks to 5 months were observed. Thirty-four received mazun, and 22 kefir. It was discovered that the average increase in weight on mazun is higher than on kefir; the amount of organic acids and ammonia on diets containing mazun and kefir is the same as for a diet containing rice water. In mixed feeding the levels of organic acids and ammonia are within normal ranges. Thus, mazun appears to be fully suitable for the mixed feeding of infants.

Effect of milk, acidified by lactic acid, upon the function of the alimentary tract in infants Materialy po vliyaniyu moloka, podkislennogo molochnoi kislotoi, na funktsiyu pishchevaritelnogo trakta u detei rannego vozrasta. GIL S. A. *Pediatriya* 1957, 7 (33-34)

Clinical observations on 30 infants (before weaning) receiving milk acidified with 0.5% lactic acid are given. Also, experimental investigations of 29 laboratory animals were carried out. It was discovered that the acidification of milk does not confer on it adequate bactericidal properties. The total acidity of the gastric content is in this case lower than when feeding with kefir; the pH is higher. Weight increase in the group which received kefir additionally was considerably larger than in children with additional milk acidified with lactic acid. It seems that artificially acidified milk can be excluded from infant feeding.

New food products for infants Novye produkty dlya detei rannego vozrasta. KOROBKINA G. S. *Pediatriya* 1957, 7 (37-40)

In 1955-56 the Institute for Nutrition of the USSR Academy of Medical Sciences studied some 170 foreign samples of food products for young children. Those investigated included: (1) Special milk for unweaned infants, consisting of cows' milk, cream and lactose. This milk can be given to infants (even premature infants) from birth. (2) Dried, half fat or defatted milk, to be used for a short time according to strict medical instructions for medical purposes. (3) Dried protein preparation 'Vazzol.' (4) Dried acidophilic milk, having a favourable effect upon gastrointestinal affections in young infants. (5) Thin 'gruel' from fine ground rice meal as extra food. (6) A flour mixture, consisting of 2 parts of rice flour, 1 part buckwheat and 1 part oatflour, with the addition of fruits or vegetables to improve the amino-acid content of gruel protein, and to increase the amount of vitamins and mineral substances. (7) Preserved fruit and vegetable mash. (8) Vitamins A and D in fruit syrups with the addition of cocoa. (9) Polyvitamin malt extract, prepared from malt, and rose hip syrup with the addition of vitamins A, B and D (for children over 6 months).

The influence of nutrition upon some functions of the infantile organism Vliyanie pitaniya na nekotorye funktsii detskogo organizma. VEDRASHKO V. F. *Pediatriya* 1957, 7 (66-68)

It was established that the best standard of general development of children, their state of wellbeing, reduced susceptibility to catarrh of the upper respiratory tract, influenza and tonsillitis was observed in cases where children of nursery age (older than 1 year) received per kg. of weight 4-4.5 g. of protein, and children of pre-school age 3.5-4 g. protein (in correct ratio to other substances). For children older than 1 year the most favourable proportions of protein, fat and carbohydrates were 1:1:3 or 1:1:4. In children of pre-school age who received 2.5 g. of protein, the same amount of fat and 15 g. of carbohydrates per kg. of child's weight with a preponderance of vegetable protein, phagocytosis and complement titre were lower than average. On a diet containing 3.5 g. of protein, 3.5 g. of fat, and 12 g. of carbohydrates per kg. of weight, and with an increase of animal protein up to 65%, these indices increased and approached normal.

Data of the physiological importance of nicotinic acid in pediatrics Dannye o fiziologicheskom znachenii nikotinovoi kisloty dlya rebenka. MAKSIMOVICH YA. B. *Pediatriya* 1957, 7 (83-85)

Observations on 300 children gave the following results: (1) The need for nicotinic acid in children is subject to seasonal variations. In summer the need is increased (exercise in the fresh air, temperature factor, etc.) (2) In the organism of children backward in neuropsychic development, a deficiency of nicotinic acid is recorded. (3) Impairment of nicotinic acid metabolism in disease depends on the degree and character of the pathological process; restoration of the metabolism is proportional to the restoration of the general state of health. In cases of nicotinic acid deficiency in the organism, the vitamin should be added to the children's food.

The vitamin B_1 metabolism in small children with acute nutritional disturbances Obmen vitamina B_1 u detei rannego vozrasta s ostrymi rasstroistvami pitaniya. MALCHENKO G. A. *Pediatriya* 1957, 7 (93-96)

The degree to which vitamin B_1 was provided was studied in 98 children aged 3-30 months who were suffering from acute nutritional disturbances; in 78 of them the vitamin B_1 metabolism was investigated repeatedly; 29 children received vitamin B_1 by way of treatment; 63 children out of the 98 were on early mixed or artificial feeding. In 61 children (out of 69) in the peak period of the disease, a marked fall of the vitamin B_1 level in the urine was found (less than 15% of the ingested amount). The height of the vitamin B_1 deficit in the organism depended on the severity, phase and duration of the illness. The normaliza-

tion of the vitamin B_1 metabolism occurred later than the clinical cure. A dose of 25 mg. vitamin B_1 per os rectified its pronounced lack in children with simple dyspepsia even when given over a limited period; 25 mg. vitamin B_1 intramuscularly both in simple and in toxic dyspepsia caused a notable improvement of the vitamin B_1 metabolism and was paralleled by a quite rapid improvement of the child's general condition.

Acute Infectious Diseases

The new antibiotics in whooping cough therapy Novye antibiotiki v lechenii koklyusha. GERASIMENKO L. I. Institute of Pediatrics, USSR Academy of Medical Sciences, Moscow *Pediatriya* 1958, 2 (51-57) Tables 4

The results are given of whooping cough treatment with antibiotics—oxytetracycline, tetracycline and chlortetracycline, administered to 288 children. Oxytetracycline and tetracycline were prescribed at 25,000-40,000 units each per kilogramme of weight. The treatment was carried out in one or two cycles. Observations showed that these antibiotics are equally effective in relation to whooping cough; further, their positive effect is the higher, the earlier treatment is begun. The influence of the antibiotics on the cough was expressed in a reduced frequency and lessened severity of the coughing spells, whereas the general duration of coughing remained the same as in children who had not been treated with antibiotics. Checking action on the development of paroxysmal coughing was not observed. The antibiotics of the tetracycline group proved quite effective in treatment of pertussal pneumonia. At the same time, the antibiotics did not prevent the development of complications, cross infections and concomitant illnesses. Proper organization of the environment surrounding the patient and administration of non-specific therapy (vitamin treatment, aerotherapy, blood transfusion, physiotherapeutic methods of treatment) are therefore necessary along with prescription of antibiotics.

The prophylaxis of whooping cough K voprosu profilaktiki koklyusha. DADASHYAN M. A. *Uch. Zap. II Mosk. Med. Inst.* 1957, 7 (167-175)

The questions of the specific prophylaxis of whooping cough in children, and of the reactogenicity of prophylactic effectiveness of the pertussis, precipitated pertussis, and pertussis-diphtheria vaccines, worked out in the Gamaleya Institute of Epidemiology and Microbiology, are considered. The results of the investigations have shown that the pertussis and precipitated pertussis vaccine (using intramuscular administration for the latter) possess feeble reactogenic properties, which are considerably less pronounced with the pertussis-diphtheria vaccine.

Microbiology, epidemiology, and prophylaxis of whooping cough Voprosy mikrobiologii, epidemiologii i profilaktiki koklyusha. SOLOVYANCHIK S. I. *Zdravookhr. Belor.* 1957, 12 (43-45)

Morbidity of pertussis amounted in Belorussia in 1955 to 26.5, and in 1956 to 21.2 per 10,000 inhabitants. For the study of the properties of the local strains of the pertussis bacillus a bacteriological examination of 300 pertussis patients and 600 contacts was conducted in Minsk. Thirty-three strains were isolated of which 26 were in phase I, 3 in phase II, and 4 in phase III. The strains in phases I and II were inert in respect of fermentation of sugars, possessed haemolytic properties, and were virulent for white mice by intraperitoneal and intranasal infection; the intradermal administration of 500 million microbial bodies evoked in rabbits areas of necrosis from 0.5 to 2 cm. in diameter. The strains in phase III did not evoke necrosis; 2 of them fermented glucose, maltose, and sucrose.

Atypical measles in children Atipichnaya kor u detei. PATUSHINSKAYA R. A. Department of Pediatrics, Pavlov Medical Institute, Ryazan *Pediatriya* 1958, 2 (61-65)

The features of atypical measles observed in 25 children were lengthened prodromal period, high temperature and pronounced toxicosis with little or no manifestations of catarrh. Conjunctivitis, rhinitis and Filatov-Koplik spots appeared or were intensified only in the eruption period. The measles rash was typical in character, localization and subsequent pigmentation, but was protracted. The change in measles symptomatology was connected with the administration of antibiotics in the incubation period and at the onset of symptoms. Of the antibiotics, chlortetracycline modifies the clinical picture of measles most of all.

Special features of the clinical picture of measles in children under 6 months of age Osobennosti klinicheskoi kartiny kori u detei v vozraste do 6 mesyatsev. VOLYNSKAYA V. A. and BUGAEVA G. P. *Pediatriya* 1956, 5 (52-54)

Observations were made on 49 children. The following aberrations from the normal course of the disease were noted: prolongation of the incubation period by 5 days, absence of Filatov-Belski (Koplik's) spots and absence of conjunctivitis, reduction of the eruptive stage to 2 days, appearance of pigmentations from the 7th to 15th day.

Course of diphtheria in patients with uncompleted antidiphtherial inoculations Techenie difterii u bolnykh s nezakonchennymi protivodifteriinymi privivkami. GRANDE V. G. Department of Infectious Diseases, Medical Institute, Karaganda *Pediatriya* 1958, 2 (33-39) Tables 6

Studies were made on 2,722 diphtheria patients, of whom 597 (21.9%) had been inoculated, 923 (33.9%) had not been inoculated and 1,202 (44.2%) had been incompletely inoculated against diphtheria. The observations showed that children with uncompleted inoculations contract diphtheria more frequently and more severely, and have complications more frequently, than do patients who have not been inoculated against diphtheria. This is explained by the said group of children having greater sensitization to the diphtheria bacillus and lowered resistance to diphtheria toxin. Among the patients who died, the children with uncompleted inoculations numbered almost twice as many as did the children who had not been inoculated at all.

Study of the influence of vitamin C on the stability of immunity to diphtheria among inoculated children Izuchenie vliyaniya vitamina C na ustoichivost immuniteta k difterii u privitykh detei. BERZIN V. V. and GLINSKAYA E. V. *Zh. Mikrob. Epid. i Immunobiol.* 1957, 12 (33-38)

After vitaminization of children conducted in the winter-spring season the percentage of positive Schick reactions was lowered from 18.4 to 5.4%. Immunization with BCG vaccine and smallpox vaccine did not lower the immunity acquired to diphtheria among the children following recent reimmunization. For retention of the immunity to diphtheria and the successful development of immunity following active immunization it is recommended that vitaminization with ascorbic acid be practised, particularly in the winter-spring season.

Influenza D in young children Gripp D sredi detei rannego vozrasta. ZHDANOV V. M., RITOVA V. V. and GOLYGINA L. A. *Vopr. Virusol.* 1957, 4 (243-247)

During the winter of 1956-1957 two outbreaks of an illness of uncertain aetiology took place in closed children's institutions in Moscow. The young children were mainly affected. Eight children died on the 2nd-3rd day. Nasopharyngeal washings obtained on the 1st-3rd days of the disease were found to contain a strain of influenza virus antigenically identical with Fusimi virus described in 1952 and with the Far East influenza virus D. In view of its epidemiological importance the inclusion of the virus described into the anti-influenzal vaccine should be considered.

Rheumatic Diseases

Some indices of the functional state of the cardiovascular system in children suffering from rheumatic disease Nekotorye pokazateli funktsionalnogo sostoyaniya serdechnososudistoi sistemy u detei, bolnykh revmatizmom. CHUCHESHKINA I. M. Pediatric Clinic, First Medical Institute, Moscow *Pediatriya* 1957, 2 (9-13)

Ninety-one children suffering from rheumatic disease were examined. The form of rheumatic disease was predominantly cardiovascular. In addition to clinical examination, the patients were subjected to determination of venous blood pressure, rate of blood flow, ECG, to breath-holding and orthostatic tests and tests with physical stress. Analysis of these data revealed that the results of functional investigation are determined chiefly by the character of the course followed by the rheumatic process and the latter's phase. ECG changes in these patients were expressed in a slight increase of the PQ and QRS intervals, prolongation of the systole and alteration in the type of ECG. Venous pressure tended to hypotension in the acute period, being replaced, in a number of cases, by hypertension as the rheumatic process settled down and then returning to normal as the patient's condition improved. The arterial pressure fluctuated much less throughout the illness than the venous pressure and there was no parallelism between the two. Determination of the rate of blood flow showed its diminution during the acute period, increase in a number of subacute cases and return to normal in the inter-attack period. The results of tests with physical stress depended on the period

of the illness. Comparison of the investigational methods used leads to the conclusion that none shows any advantage over the rest; it is essential to combine several functional tests in order to discover the properties of the pathological process and the degree of functional impairment. The largest number of deviations from the normal in the functional tests was observed in the acute and subacute periods of rheumatic disease, as well as in children who had had a recent history of tonsillitis, influenza, etc. In the case of these children the deviations from the normal occurred in both directions evidently indicating instability of the nervous regulation of circulation.

Clinical and pathogenetic features of rheumatism in adolescents Klinicheskie i patogeneticheskie osobennosti revmatizma u podrostkov. KALYUZHNAYA R. A. Institute of Pediatrics, USSR Academy of Medical Sciences, Moscow *Pediatriya* 1957, 12 (9-17) Illus. 2 Tables 3

A detailed clinical examination of 45 adolescents was made with subsequent follow-up observation of them during 4 years. Further, the case records were studied of 247 adolescents who had been treated in the cardiological clinic of the USSR Academy of Medical Sciences, and an analysis was also made of the case histories of adolescents who had died of rheumatism in various clinics of Moscow from 1953 to 1955 inclusive. It was established that in this group of youngsters rheumatism is most frequently (66% of cases) a continuation of an illness that developed at the age of 6 to 9 years and in the period of puberty assumed a very serious course. However, rheumatism often begins in the adolescent period and from the very outset has a serious course. Rheumatism in adolescents frequently assumes the character of a continuously relapsing course with the result that blood circulatory disorders and cirrhosis of the liver are rapidly developed. The singularity of rheumatism at this age is that more frequently than in other age groups, apart from a continuously relapsing course, forms proceeding without attacks are observed which lead not only to deformation of the mitral valve but frequently also in insufficiency of the aortic valve. Insufficiency of the aortic valves occurs a great deal more frequently in adolescents than in younger children, which is apparently to be explained by the anatomical and physiological features of the heart and blood vessels at this age. Noteworthy among the clinical picture features of rheumatism in adolescents are marked disorders on the part of the nervous system: headaches, fatigability, impairment of memory, etc. Frequently manifest in these children is a tendency to hypertension, which is not a feature of the course of disease in other age groups. The high frequency of complaints of pains in the heart region among adolescents should be noted; this is due to dystrophic processes in the heart muscle. In the electrocardiographic study, this is expressed in variation of T-waves in standard and thoracic leads. Unlike rheumatic sclerotic lesions of the myocardium this manifestation is reversible. A tendency to angiospastic reactions and high tonus of the sympathetic nervous system also contribute to the occurrence of pains in the heart. The period between attacks is characterized in adolescents by endocrine-vegetative dysfunctions and age-conditioned functional disorders of the heart and blood vessels. Physical exercise carried out under the control of functional tests and ECG has a good effect. This should be taken into account when prescribing treatment for adolescents in the period between attacks of rheumatism and in cases where the disease runs a course without attacks.

Dynamics of motor chronaxie in children with rheumatism during treatment with ultraviolet rays Dinamika dvigatelnoi khronaksii u detei, bolnykh revmatizmom, pri lechenii ultrafioletovymi luchami. TALANOVA I. N. *Vopr. Kurort.* 1957, 4 (26-31)

By the clinical chronaximetric method the effect was studied of UV rays on the functional state of the central nervous system in 36 children ill with rheumatism. Twenty of the children were treated only with medicinal means, while 16 were additionally treated by UV irradiation. Signs of endomyocarditis were detected in all children, and acute rheumatic polyarthritis in some of them. The most significant pathological shifts of chronaxie were found in patients with severe forms of rheumatism and predominantly in children with weak and unbalanced nervous processes. Under the influence of the treatment, improvement set in of the patient's condition and the indices of chronaxie became normal, first of all in the children subjected to irradiation (after 3 to 4 exposures). The beneficial effect of UV irradiations on the functional state of the central nervous system is stressed.

Parasitic, Mycotic Diseases

The problem of toxoplasmosis Toksoplazmoz kak problema meditsiny. VILDFYUR G. *Pediatriya* 1957, 8 (12-18)

The problems of epidemiology, aetiology, pathogenesis, clinical features, diagnosis, treatment and prophylaxis are elucidated.

Some contraindications to the treatment of ankylostomiasis with carbon tetrachloride O nekotorykh protivpokazaniyakh k lecheniyu bolnykh ankilostomidozami chetyrekhkhloristym uglerodom. ZENAISHVILI O. P. *Med. Parazit. i Parazit. Bol.* 1956, 25 (297-301)

The expulsion therapy of worms in ascariasis and ankylostomiasis may give rise to a severe intoxication. In the Georgian SSR in the years 1953 to 1955 there were 3 cases of fatal poisoning of children through absorption of the products of metabolism of the drug and of the toxins of ascarids killed with carbon tetrachloride. Experience has shown that acute poisoning may be associated with the deficiency of calcium in the blood occurring in pregnancy, during lactation and in hyperthyroidism. These 3 conditions should be included in the list of contraindications to the treatment of ankylostomiasis with carbon tetrachloride. In a simultaneous infestation with ascarides and ankylostome worms the former should be attacked first, and the latter 12 to 14 days later.

Lambliasis in young children according to records of the diagnostic department Lyamblioz u detei rannego vozrasta po materialam diagnosticheskogo otdeleniya. SHATILOVA A. P. *Vopr. Okhr. Mater. i Dets.* 1957, 3 (40-43)

Observations on 129 children showed that the most important clinical symptoms of lambliasis (giardiasis) are intestinal disturbances, green liquid and semiliquid stools, with mucus and particles of undigested food. Lamblia cysts frequently in combination with vegetative forms were found in the faeces. A small number of children showed a slight enlargement of the liver and spleen. Marasmus, anaemia, eosinophilia and monocytopenia are observed. The disease is characterized by a protracted recurrential course. It is established that dysentery, combined with lambliasis, follows a protracted course with discharge of bacteria, and slow normalization of the stools, and is often accompanied by wasting and hypochromic anaemia.

Surgery, Roentgenology

Prophylaxis and treatment of sequelae of poliomyelitis Nekotorye voprosy profilaktiki i lecheniya posledstvii poliomyelita. NOVOZHILOV D. A. *Ortop. Travm. i Protez.* 1957, 5 (15-22)

A report is issued on the treatment of 2,000 children, both during convalescence and suffering from residual defects of poliomyelitis. Absolute rest on a flat bed with the limbs in a comfortable position is imperative in the acute stage. Immobilization of the limbs, physiotherapeutic exercises and thermal treatment are recommended after the disappearance of pain. Contractures may be overcome by extension of the contracted muscles. If this fails, surgical interference is indicated: in muscular paralysis—arthrodesis, in stationary flexion contractures of the knee joint—supracondylar osteotomy with the subsequent use of an orthopaedic appliance. To replace paralysed extensors of the leg, a bilateral transplantation of still functioning flexors is recommended. This operation is contra-indicated where the contracture is 170°. Transplantation of the foot muscles should be combined with arthrodesis. Where the leg is shortened, osteotomy of the tibia and fibula is performed with subsequent extension.

Social Medicine, Prevention, Organization

Propaganda among parents on the correct nursing and feeding of children Metodika propagandy sredi roditelei voprosov ratsionalnogo vskarmlivaniya i pitaniya detei KARMANOVA E. G. and ZBOROVSKAYA F. I. *Pediatriya* 1957, 7 (46-49)

The following methods of propaganda among parents, on the problems of the correct feeding and rearing of children, are suggested: the organization of schools for young mothers; demonstration of the preparation of fruit dishes and juice; systematic training of mothers in hospitals where the mothers remain with the infants; health-educational propaganda for older children, and also in doctors' consulting rooms, out-patients departments, nurseries and hospital wards; the organization of training schools for domestic workers taking care of small children; propaganda on correct feeding in milk distribution centres; the inviting of eminent specialists to initiate popular scientific literature, films, and the publication of journals on problems of the care, upbringing and feeding of children.

News and Comment

GENERAL NEWS

Unrestricted Grants for Medical Education.—Unrestricted grants totaling $1,650,000 to eleven private medical schools in support of their teaching-research staff were announced on May 26 by the Josiah Macy, Jr. Foundation. The action was taken in recognition of the fact that the adequate staffing of medical schools is the crucial problem of the national program of medical research and teaching.

Dr. Willard C. Rappleye, President of the Foundation made the following comments concerning these grants:

"Medical education in this country is in a critical phase. Because of their widening obligations, the enormous growth of medical science, inflation, and other factors the medical schools have increasing difficulty in securing sufficient support to carry out the functions which they are called upon to perform. It is difficult to recruit and hold a teaching faculty because of the financial opportunities in private practice, industry, and government employment.

"In contrast with the situation 10 years ago, large amounts of money are now available for categorical, project, and program grants for a wide variety of medical and allied research and for fellowships and traineeships. The National Institutes of Health award many research grants and fellowships. Millions of dollars are available annually from that source. Industry is increasing its contributions to medical research. The national foundations, constantly increasing in numbers and covering almost every field of health and medical investigation, are expanding their aid for specific projects. The problem of necessary facilities for research is slowly being solved, partly by government grants for construction. Several private foundations may shortly help also. There are now more funds for medical research than there are facilities and permanent staff to carry out the programs. The recruitment and training of permanent teachers and staff members are essential if the supply of well-qualified physicians and investigators for the future needs of the country is to be maintained.

"The uncertainties of the entire effort so vital to the national welfare are the scientific and teaching staffs. Means must be found to stabilize and strengthen the hard core of the medical school faculties, particularly in the basic medical sciences. The National Fund for Medical Education, the American Medical Education Foundation, the alumni of the medical schools and the use by medical schools of professional fees from private practice and medical insurance are helping to finance medical education. Recently a new potential source of assistance has begun to appear in the local health foundations created under the United Funds and Councils of America. All of these efforts are aimed at seeking unrestricted funds for medical schools. Because medical education and research are essential for the future health and safety of the nation, it is now proposed that the Federal government through one of several methods begin to make appropriations for part of the support of medical schools. This action, if taken, would be in addition to, or in time may absorb, project and program grants from that source.

"In view of the present serious threat to medical education and the possibility of substantial assistance toward a firm basis of support being found in the near future, the Josiah Macy, Jr. Foundation has made unrestricted grants of $50,000 per annum for a three-year period to each of eleven private medical schools for strengthening their research-teaching staff, particularly in the medical science departments, the money to be spent as each institution elects. This interim assistance will help a few private medical schools during the period that efforts are being developed to secure support of a permanent character."

The medical schools to which the unrestricted grants were made are as follows:

Yale University School of Medicine
University of Chicago, The School of Medicine
The Johns Hopkins University School of Medicine
Harvard Medical School
Washington University School of Medicine
Columbia University College of Physicians and Surgeons
Cornell University Medical College

New York University College of Medicine
University of Rochester School of Medicine and Dentistry
Vanderbilt University School of Medicine
Duke University School of Medicine

ANNOUNCEMENTS

Mead Johnson Grants for Pediatric Research.—The Awards Committee for the Mead Johnson Program for Pediatric Research of the American Academy of Pediatrics announces the availability for the coming year of funds to provide financial aid to young pediatric research workers. These funds have been provided each year since 1958 by Mead Johnson & Company under rules established by the Academy's Awards Committee. The maximum amount for any one grant in any year is $3,500. Grant applicants should be young pediatricians who are not more than 10 years beyond the completion of their residency. These grants are specifically intended to encourage the young, unestablished, research-minded, academic pediatrician. Deadline for receipt of grant applications for July, 1960, will be January 15, 1960.

Interested persons should write to American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill.

Continuation Course in Pediatrics.—On Sept. 22 to 24, 1959, the University of Minnesota will present a Continuation Course in Pediatrics for Pediatricians at the Center for Continuation Study on the University campus. This course for pediatricians and physicians interested in the field of pediatrics consists of lectures, panels, and round-table discussions on general pediatrics, with particular emphasis on developmental neurology, endocrinology, and genetics, as well as child psychiatry.

Visiting faculty will include Dr. Carl A. Genzell, Professor of Obstetrics and Gynecology, Konung Gustaf V Forskningsinstitut, Stockholm; Dr. L. Emmett Holt, Jr., Professor and Head, Department of Pediatrics, New York University College of Medicine; Dr. Leo Kanner, Professor of Child Psychiatry, Johns Hopkins University, and Visiting Professor of Child Psychiatry, University of Minnesota; Dr. Jack Metcoff, Professor and Chairman of Pediatrics, University of Illinois College of Medicine, and Professor of Pediatrics, Northwestern Medical School, and Dr. Irvine McQuarrie, Professor Emeritus, Department of Pediatrics, University of Minnesota, and Director of Research, East Bay Children's Hospital, Oakland. Dr. Holt will also present the Fifth Irvine McQuarrie Lecture at 8:15 p. m., Wednesday, Sept. 23. The course will be presented under the direction of Dr. John A. Anderson, Professor and Head, Department of Pediatrics. The remainder of the faculty will include members of the faculty of the University of Minnesota Medical School and the Mayo Foundation. Lodging and meal accommodations are available at the Center for Continuation Study.

Books

BOOK REVIEWS

Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment. By H. J. Parish, M.D., F.R.C.P.E., D.P.H. Price, $7. Pp. 256, with 31 illustrations. E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh (The Williams & Wilkins Company, Baltimore, exclusive U. S. agents), 1958.

An excellent compilation of the methods of preparation and use of the biological preparations. The author succeeds admirably in making the principles of immunology and their practical application clear and concise. Some of the preparations described are not familiar to the American medical profession, since the author is British and he presents the methods and preparations in use in Britain. The book is well illustrated, easy to read and to use as reference. It includes a good historical summary of immunology and good basic bibliography.

SUSAN C. DEES, M.D.

Embryonic Nutrition. Edited by Dorothea Rudnick. Price, $3.25. Pp. 112, with 34 illustrations. The University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1959.

One of 10 volumes comprising a record of the Developmental Biology Conference Series held in 1956 under the auspices of the National Academy of Sciences-National Research Council, this book is composed of six papers dealing with the biochemical aspects of embryonic nutrition.

An interesting discussion of energy distribution in embryonic growth, differentiation, maintenance and functional activity is presented in a paper entitled "Embryonic Energy Exchange," by E. J. Boell. A chapter on "Metabolic Patterns in the Sea Urchin Embryo," by J. Lee Kavanau, again illustrates the value of this material in the quantitative investigation of embryonic metabolic processes; in this instance, exploratory studies into possible interrelationships between certain of the B vitamins and protein synthesis. "Yoke Utilization in Fishes," by Sydney Smith, is an excellent paper summarizing the author's vast experience in this area, in which the trout has been an ideal species for investigation. Immunobiological and immunochemical concepts of embryonic growth and differentiation are introduced in the paper "antigens as Tracers of Embryonic Synthesis," by James D. Ebert, in which the antigenic properties of embryonic tissues are discussed. Differences in quantitative demands upon the embryonic energy-substrate supply mechanism with the basic types of developmental activity are outlined in a chapter dealing with "Nutrient Necessities in Chick Development," by Nelson T. Spratt Jr., and in the final section, "Enzymes: Formation and Growth," Florence Moog presents a review of the problems relative to enzyme patterns in differentiating tissue.

Adequate introductory material prefaces most of these papers, and well-edited comments from the discussion on each are included, in several instances adding substantially to the intended interdisciplinary aura.

ROBERT STEMPFEL JR., M.D.

Affections non congénitales de l'annus et du rectum chez l'enfant. By Jean Duhamel. Price, 3,600 fr. Pp. 264, with 110 illustrations. Masson & Cie, 120 boulevard Saint-Germain, Paris 6°, 1958.

This well-organized volume, based on 450 consultations carried out by the author at the Hôpital des Enfants-Malades in Paris, discusses the anorectal anatomy of the child, the technique and indications for endoscopy, and the relative frequency of anorectal disorders in children. Separate chapters cover vascular disorders (angiomas and hemorrhoids), ulcerations, cryptitis, venereal infections, fissures, rectal infections, mucous prolapse, encopresis, constipation, polyps, and malignant tumors. The illustrations are very good, and the therapy recommended is sensible. Each chapter is headed by a brief summary of its contents, and there is an excellent bibliography of the world literature. This book would be a valuable addition to the library of any physician doing endoscopy or anorectal surgery in children, and would be of interest to the general pediatrician.

JEANA LEVINTHAL, M.D.

TWO CUTTER SPECIFICS TO MEET YOUR NEEDS

specific
for whooping cough prophylaxis or treatment

Hypertussis®

Pertussis immune globulin derived from human venous blood

- highly purified globulin fraction of venous blood from healthy professional donors hyperimmunized with Cutter Phase I Pertussis Vaccine
- as reaction-free as gamma globulin derived from human venous blood
- small dosage volume lessens tissue distention
- highly concentrated—1¼ cc. contains the gamma globulin equivalent of 25 cc. human hyperimmune serum
- no reconstitution required, ready for immediate use

specific
for immunization of adolescents and adults

Adult Dip-Tet* Alhydrox®

Diphtheria-Tetanus Toxoid Combination

- significant, measurable immune response[1]
- booster shots for adolescents and adults with less risk of excessive reactivity
- primary immunization from 8 to 80 with far fewer serious reactions
- high purification of both components reduces reactivity
- adsorption on Alhydrox [$Al(OH)_3$] retards absorption rate, minimizes reactions

*TM

1. Edsall, G.; Altman, J. S., and Gaspar, A. J.: Am. J. Pub. Health, 44: 1597, 1954.

For complete information on these two Cutter specifics see PDR page 622, ask your Cutter man or write to Dept. 9-12J

CUTTER

CUTTER LABORATORIES • Berkeley, California

VARAMEL
BENEFITS
■ Better tolerance; no sour odor at regurgitation (butterfat replaced with coconut and corn oils).
■ Optimum caloric efficiency and protection of skin integrity (linoleic acid 6% of calories).
■ Protection against iron deficiency anemia (7.5 mg. of iron per quart at 1:1 dilution).
■ Daily vitamin intake assured (Varamel provides Recommended Daily Allowances of all essential vitamins).
OPTIMUM
NUTRITION
Providing all the normal dietary requirements plus a reserve for stress situations.

IF YOU PREFER
A FLEXIBLE
FORMULA

VARAMEL

GIVES YOU ALL
THESE BENEFITS
PLUS
CARBOHYDRATE
CONTROL

Varamel supplies 32 calories per ounce. The physician adds water and carbohydrate to meet the needs of the infant. The usual dilution is one part Varamel to one part water plus carbohydrate to make a 20-calorie-per-ounce formula.

THE BAKER LABORATORIES, INC.
Makers of Baker's Modified Milk
Cleveland 3, Ohio

a new form of SIMILAC®

when iron is indicated in infancy

SIMILAC WITH IRON®

12 mg of ferrous iron per quart of formula

in the yellow can

Sound infant nutrition
+
assured iron intake

for: maintenance of iron stores
prophylaxis against iron deficiency

Powder
Cans of 1 lb., with measuring cup

Liquid
Cans containing 13 fl. oz.

RESEARCH · SERVICE · NUTRITION · Ross

ROSS LABORATORIES Columbus 16, Ohio

VERSATILE FURACIN

effective by intrapleural instillation[1]

the situation: Four-month-old infant with staphylococcal pneumonia and empyema resistant to most antibiotics was allergic to antibiotic chosen after sensitivity tests. Thoracentesis produced 30-40 cc. of creamy, purulent fluid. Organism was Staphylococcus aureus, coagulase positive.

then Furacin was instilled: 0.2% Solution was diluted equally with physiologic saline and 10 cc. of mixture instilled twice daily into pleural space, with suction catheter clamped off for 1 hour. Fluid almost immediately became thinner and less viscous. Twenty-four hours later infant was less irritable, voluntarily started taking food. Instillations stopped. FURADANTIN® (brand of nitrofurantoin) Oral Suspension prescribed. Recovery uneventful.

1. Perkins, J. L.: Kansas State M. J. (to be published).

FURACIN®

brand of nitrofurazone

FURACIN has been in clinical use for more than 13 years. Today it is the most widely prescribed single topical antibacterial agent. Like other nitrofurans, FURACIN remains effective, even in pus, sera or exudates, against pathogens which have developed—or are prone to develop—resistance to antibiotics.

FURACIN, in a water-miscible base of polyethylene glycols, is available in a number of dosage forms. Included are Soluble Dressing, Soluble Powder, Solution and Cream. Also in Vaginal Suppositories, Inserts, and in special formulations for eye, ear and nose.

NITROFURANS—a unique class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

one of baby's first solid foods

is tasty "Junket" rennet-custard...supplies all the nutrients of milk and is more readily assimilable.

junket.
RENNET POWDER
makes fresh milk into rennet-custards
—7 tempting flavors

"JUNKET" Reg. U.S. Pat. Off. for rennet and other food products mfd. by Salada-Shirriff-Horsey Inc.

Here are several booklets on mental hygiene that may prove of interest and use to you and your patients.

EMOTIONAL HEALTH IN WORK AND PLAY
T. R. Retlaw, 8 pages, 15 cents

HYPNOTISM—HUMBUG OR HEALING
James A. Brussel, 6 pages, 10 cents

YOUR STAKE IN MENTAL HEALTH
George S. Stevenson, 4 pages, 10 cents

THE PSYCHIATRIST Edward Dengrove and Doris Kulman, 6 pages, 10 cents

BOOKLETS ON MENTAL HYGIENE

Keep a supply of these booklets on hand. Available at lower cost for quantity purchases.

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street • Chicago 10 • Illinois

A. M. A.
AMERICAN JOURNAL OF DISEASES OF CHILDREN

integrate your knowledge—subscribe to

↓
A. M. A. Archives of PATHOLOGY
↓
A. M. A. Archives of INTERNAL MEDICINE
↓
A. M. A. Archives of OPHTHALMOLOGY
↓
A. M. A. Archives of OTOLARYNGOLOGY

For a more complete reference shelf, we recommend these related journals. The variety of fields covered are especially appealing to the general practitioner with special interests. Each issue is important to your practice. Begin your subscriptions TODAY.

Department (D. C.)
AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St.
Chicago 10, Ill.

Begin my subscription(s) NOW, for:

A. M. A. .....

NAME .....

STREET .....

CITY .....STATE .....

For CONSTIPATED BABIES and CHILDREN

Borcherdt's

MALT SOUP EXTRACT

(MALTSUPEX)

It's not a drug—it's a food supplement. It helps nature function normally by promoting favorable aciduric bacteria in the lower tract and creates and maintains soft natural stools.

Malt Soup Extract is a non-diastatic barley malt extract neutralized with potassium carbonate. It's harmless and, when necessary, can be given over a long period of time without any side effects. It causes no inflammation, no gas pains and restores a normal acid condition in the lower tract.

For babies two tablespoonfuls of Malt Soup Extract is added to the formula. For children two tablespoonfuls in milk (children love it) twice a day or use it on cereals or in fruit juice.

Some physicians prefer the liquid form. Many like the mild tasting, easily handled powder form. Both are available at drug stores coast to coast.

"8 oz. and 16 oz. bottles"

Borcherdt Company

217 North Wolcott Avenue, Chicago 12, Illinois

In Canada, Chemo Drug Co., Ltd., Toronto, Canada

We will be glad to send you clinical samples of powder and (or) liquid.

Serving the Medical Profession
SINCE 1868

Borcherdt Company B & C
217 N. Wolcott Ave., Chicago 12, Ill.
Gentlemen: Please send me sample of Malt Soup Extract (☐ Powder ☐ Liquid) and literature.

_____ M.D.

Address _____

City _____ Zone ____ State _____

10 SPECIALTY JOURNALS

PUBLISHED MONTHLY
BY THE AMERICAN MEDICAL ASSOCIATION

NEUROLOGY

GENERAL PSYCHIATRY

SURGERY

PATHOLOGY

DISEASES OF CHILDREN

OPHTHALMOLOGY

INDUSTRIAL HEALTH

DERMATOLOGY

INTERNAL MEDICINE

OTOLARYNGOLOGY

Each journal offers the latest medical research and developments of outstanding specialists. Edited for the doctor by prominent authorities in each special field, these journals are of value not only to the specialist but to the general practitioner as well.
To order your subscription to one of the A.M.A.'s specialty journals use the form below.

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn • Chicago 10

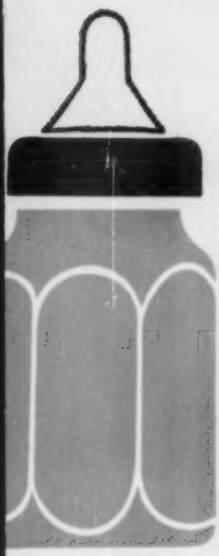
Please enter my subscription to the specialty journal checked at right.
Remittance for ☐ one year ☐ two years is enclosed.

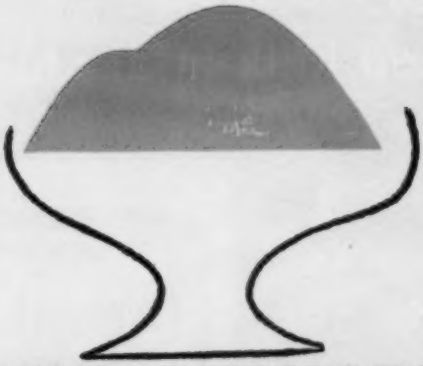
NAME_____

ADDRESS_____

CITY_____ ZONE____ STATE_____

(One year rates)	U.S.A. & Possessions APO's	Canada	Outside U.S.A. & Possessions
☐ A.M.A. Arch. Neurology	$14.00	$14.50	$15.50
☐ A.M.A. Arch. Gen. Psychiatry	$14.00	$14.50	$15.50
☐ A.M.A. Arch. Dermatology	12.00	12.50	13.50
☐ A.M.A. Arch. Industrial Health	10.00	10.50	11.50
☐ A.M.A. Arch. Internal Medicine	10.00	10.50	11.50
☐ A.M.A. Jrl. Diseases of Children	12.00	12.50	13.50
☐ A.M.A. Arch. Surgery	14.00	14.50	15.50
☐ A.M.A. Arch. Pathology	10.00	10.50	11.50
☐ A.M.A. Arch. Ophthalmology	12.00	12.50	13.50
☐ A.M.A. Arch. Otolaryngology	14.00	14.50	15.50





WHY ORANGE?

PALADAC®

liquid multivitamin formula

is orange in color, aroma, and flavor because orange has specific meaning for children. From the time they first taste orange juice and later learn to enjoy orange-flavored drinks, orange ice, and orange candy, orange is a universal favorite—appealing, palatable, highly acceptable.

PALADAC is a 9-vitamin formula that is even-flowing, readily miscible, if desired, with milk, fruit juice, or other foods, and is stable, requiring no refrigeration.

Each 4-cc. teaspoonful of PALADAC supplies:

Vitamin A	5,000 units
Vitamin B_1 (thiamine hydrochloride)	3 mg.
Vitamin B_2 (riboflavin)	3 mg.
Nicotinamide (niacinamide)	20 mg.
Vitamin B_6 (pyridoxine hydrochloride)	1 mg.
Pantothenic acid (as the sodium salt)	5 mg.
Vitamin B_{12} (crystalline)	5 mcg.
Vitamin C (ascorbic acid)	50 mg.
Vitamin D	1,000 units

Available in 4-ounce and 16-ounce bottles.

PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN

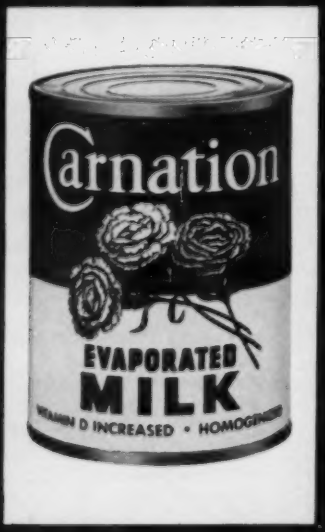
Now 2 ways to specify Carnation Evaporated Milk infant formula

1 NEW! CARNALAC

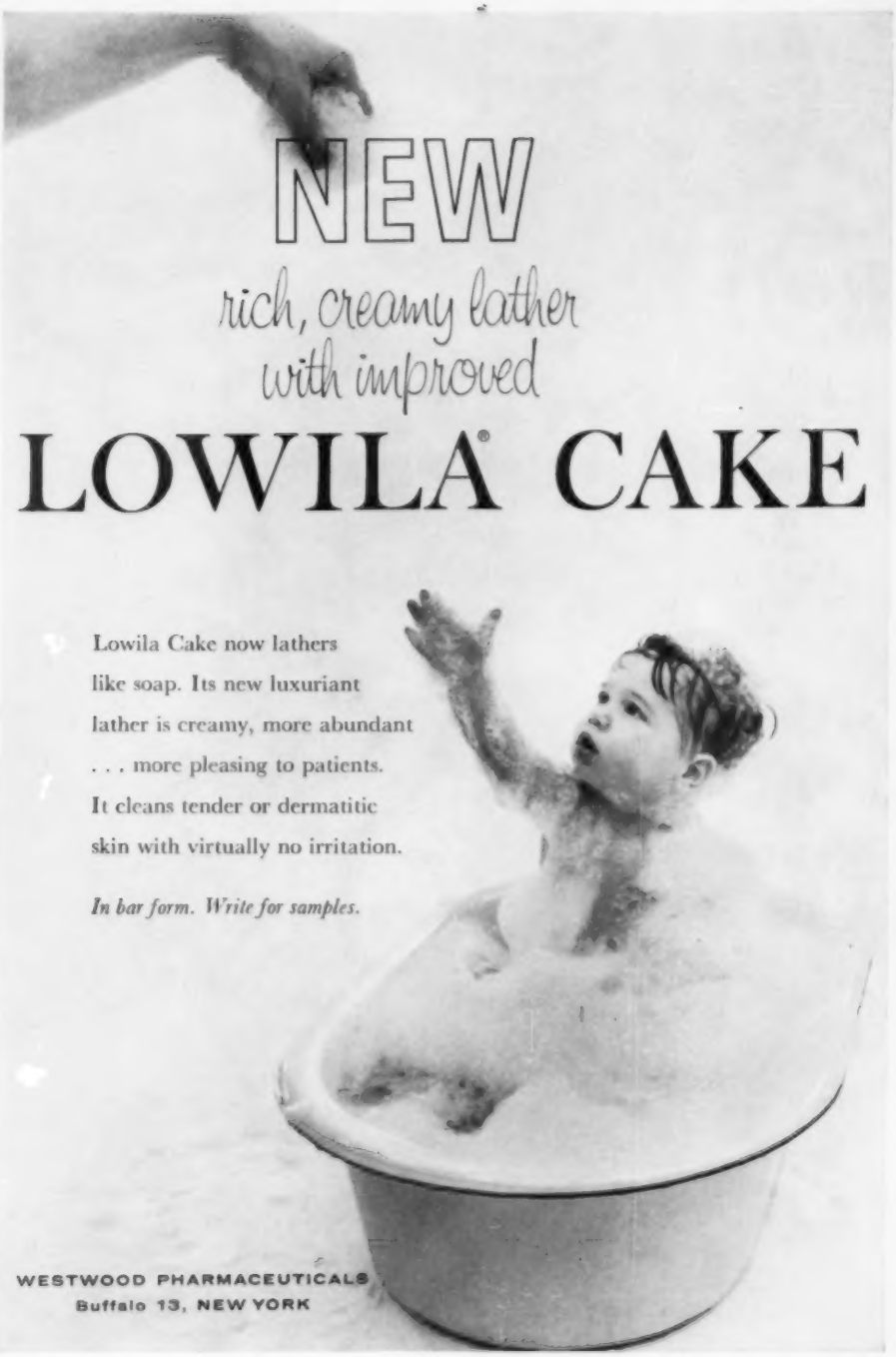
...when maximum convenience is desired. New Carnalac is Carnation Evaporated Milk with carbohydrate and Vitamin D added. Diluted 1:1, it provides the typical Carnation Evaporated Milk formula as usually prepared at home.

2 CARNATION EVAPORATED MILK

...when maximum formula flexibility is desirable for the baby... or when maximum economy is necessary for young parents.



DETROIT 32, MICHIGAN



NEW

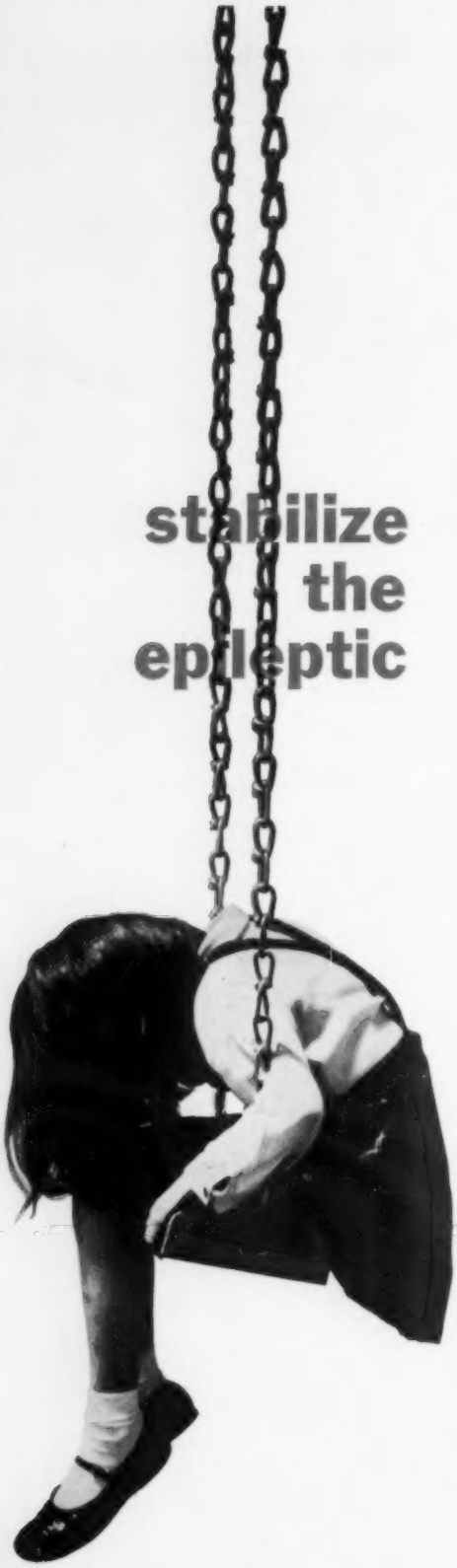
rich, creamy lather
with improved

LOWILA® CAKE

Lowila Cake now lathers like soap. Its new luxuriant lather is creamy, more abundant . . . more pleasing to patients. It cleans tender or dermatitic skin with virtually no irritation.

In bar form. Write for samples.

WESTWOOD PHARMACEUTICALS
Buffalo 13, NEW YORK



stabilize the epileptic

Better control of seizures and better understanding by parents before a child starts school help a great deal to establish a stable, normal outlook in the epileptic.

Highly effective: In most types of seizures, especially major motor seizures, **MEBARAL** is one of the best-tolerated anticonvulsants for children. This antiepileptic does not tend to lower learning capacity.

Unsurpassed safety: Mebaral is not likely to cause hyperactivity in young children. Toxic reactions or ill effects from it are rare.

MEBROIN®, combining Mebaral and diphenylhydantoin, is synergistic—and side effects are infrequent. Each relatively tasteless Mebroin tablet contains 90 mg. Mebaral and 60 mg. diphenylhydantoin. Mebroin brings maximal control of seizures with minimal toxicity.

Mebaral dosage: CHILDREN under 5 years, from ¼ to ½ grain three or four times daily; over 5 years, from ½ to 1 grain three or four times daily. ADULTS, from 6 to 9 grains daily.

Mebroin dosage: CHILDREN under 6 years, ½ tablet once or twice daily; over 6 years, 1 tablet two or three times daily. ADULTS, 1 or 2 tablets three times daily (average dosage).

For epilepsy at any age

MEBARAL®

Supplied: **MEBARAL** tasteless tablets of 200 mg. (3 grains), 100 mg. (1½ grains), 50 mg. (¾ grain), 32 mg. (½ grain). Bottles of 100.

MEBROIN virtually tasteless tablets. Bottles of 100.

Winthrop LABORATORIES NEW YORK 18, N. Y.

Mebaral (brand of mephobarbital) and Mebroin, trademarks reg. U. S. Pat. Off.